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TITLE: Building a Better Model: A Personalized Breast Cancer Risk Model Incorporating Breast Density to Stratify Risk and Improve Application of Resources

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14. ABSTRACT Purpose: Development and validation of a personalized breast cancer risk assessment model that includes automated measurement of breast density. Scope: Assemble a cohort of women with known breast cancer risk factors and digital mammogram files for women diagnosed with breast cancer using existing data sources and match them to controls (Harvey/Knaus). Validate and refine automated breast density software (Yaffe/Harvey). Build and validate the initial comprehensive model (Knaus/Yaffe/Harvey). Major Findings: During this second year, we have recruited over 3200 women (622 cases). Breast density measurement has been evaluated for accuracy using a second test set showing very good correlation with 2D methods, for precision using repeated measures with excellent correlation, and variation between vendors. A survey instrument was developed, vetted using focus groups, and administered (nearing completion) to evaluate screening knowledge, practices, and willingness to change practice.				
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1. INTRODUCTION:

This project is aimed at meeting informational needs by moving the nation from guidelines based on population averages to recommendations based on an individual's risk beginning with personalized mammography screening decisions. This will be done by increasing the ability to predict a women's risk of developing breast cancer by adding a strong risk factor—breast density—to current risk-assessment equations or algorithms. Our plan is, over three years, to build and initially validate a comprehensive breast cancer risk model. The overall work will require the recruitment of 1000 cases (breast cancer patients) and 3000 controls (non-breast cancer patients) from whom we will collect extensive risk factor information and breast density based on digital mammograms previously obtained at UVa. Breast cancer risk information is largely already available for cases though patients will be requested to validate and complete data. The recruitment of 3000 control patients will require engagement with the community through appropriate messaging and marketing. The measurement of breast density using automated methods will be optimized during this study through the evaluation of outlier correction, comparison of several different software methods, precision measurement, and evaluation of variation by mammography machine vendor. Once the model is complete, tested nationally, and proven accurate, it will be available for widespread use within five to six years.

2. KEYWORDS: Breast cancer; risk model; mammography; breast density

3. OVERALL PROJECT SUMMARY: This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported.

Task 1: Develop procedures for team communication and coordination (month 1)

Completed. A listserve was developed for the group early on. Bi-weekly conference calls were held on Tuesdays at noon. An agenda preceded each call by at least one day. Quarterly Team meetings were held at UVa (12 Dec 2011, 16 March 2012, 05 June 2011, 4 Dec 2012, 8 March 2013, 17 June 2013, 9 Dec 2013, 24 March 2014, 12 June 2014). Bi-annual team meetings were held, alternating at UVa (09Sept 2011, 24 Sep 2012, 23 Sep 2013, 12 May 2014) and Toronto (20 April 2012, 03 May 2012, 16 Sept 2014). All PIs, advocates, and key personnel attended these meetings.

Task 2: Submit protocol to Institutional Review Board/Human Investigation Committee (months 1-3)

Completed. Study protocol, consent, and recruitment materials were drafted, submitted to UVa IRB and to DoD for review. All were approved. The UVa IRB reviews all open protocols and consent forms annually; once approval has been received locally, the updated documents were sent to DoD for their review and approval. All annual reviews have been completed.

Task 3: Establish secure database (months 1-2)

Completed. A secure database was established behind a secure firewall. The database is HIPAA compliant. Data fields and dictionary were defined. Minor changes were made to clarify choices. Data linkages were validated. Data was successfully extracted with a small number of unanswered items. These primarily related to details about breast cancer diagnosis (histologic type, grade, etc.). These data were entered using our Breast Cancer Database and Clinical Data Repository in an ongoing fashion.

Task 4: Perform outlier correction for 3D Cumulus (Cumulus V) (months 2-6)

Completed. The first round of outlier correction was completed during Year 1. Cumulus V was used to analyze a set of 260 mammograms for volumetric density, and those results were compared with estimations of area density made by Dr. Harvey using our two-dimensional Cumulus 2D area method. During a work visit to Toronto from October 29 to November 3, 2011 Dr. Harvey evaluated any discordant readings using color maps to visually correlate the density map with the mammographic image. In January 2012, Olivier Alonzo-Proulx performed calibration of the seven mammography units at UVA, including three units at the Breast Care Center, three units at the Northridge site, the mobile van unit, and one system at Orange Medical Center. Both the detectors and the thickness readout mechanisms were characterized on each of the units in order to make retrospective and prospective volumetric breast density measurements.

Further modifications were made to the density algorithm and the images were reevaluated. The new data were reviewed during Dr. Harvey's visit to Toronto (16 Apr to 20 Apr 2012). Results are shown in Figure 1 and demonstrate an improved correlation between the gold standard Cumulus 2D and CumulusV. Correlations were also made using Volpara, a commercially available volumetric density measurement tool. Results are shown in Figure 2 where the correlation between the two algorithms is seen to be quite high. The Volpara measurement systematically indicates lower volume, since it excludes the contribution of skin.

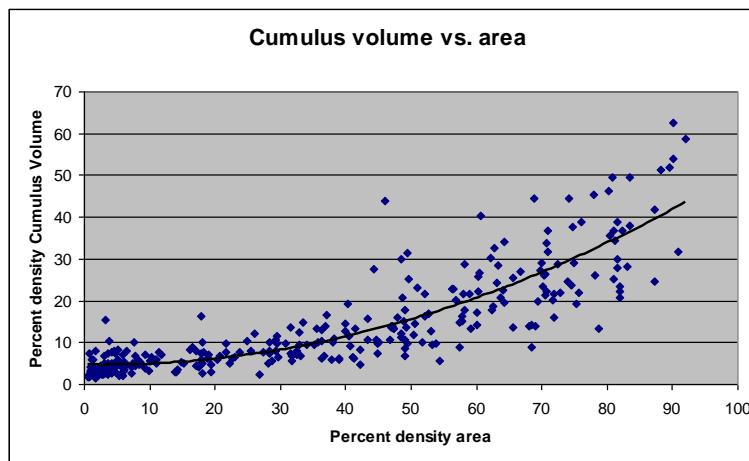


Figure 1: Cumulus 2D area (measured by Dr. Harvey) density vs. Cumulus V volume. The quadratic correlation is R= 0.87.

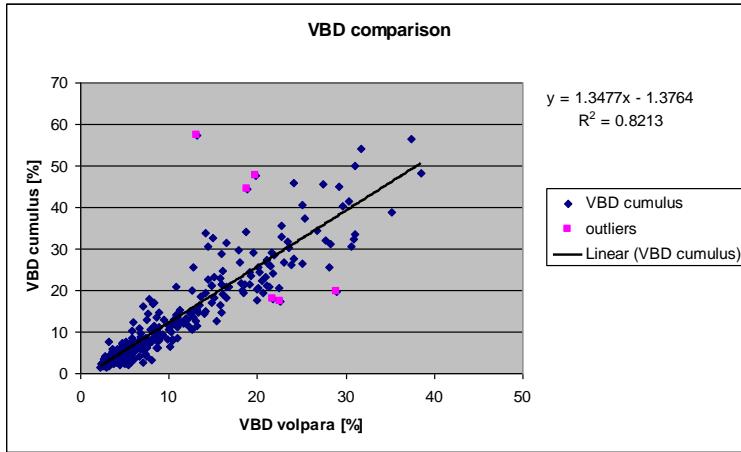


Figure 2: CumulusV volume vs. Volpara volume

A limitation of the above dataset is the fact that the mammograms were acquired over a long period of time, during which the machines may have been serviced or altered. Several detectors have been replaced since those images were obtained and this may have resulted in the calibration not representing the actual state of the imaging system at the time that the mammograms were acquired.

Second dataset. To test CumulusV using more recent mammograms, a new dataset was collected and retesting was completed during Year 2. The new dataset included 100 images from a GE unit and 100 images from a Hologic unit. These were reviewed during Dr. Harvey's visit to Toronto October 2012. The three volumetric methods (CumulusV, Volpara, Quantra) were compared to the gold standard area based method, Cumulus 2D (Figures 3-5). Volpara had the best correlation.

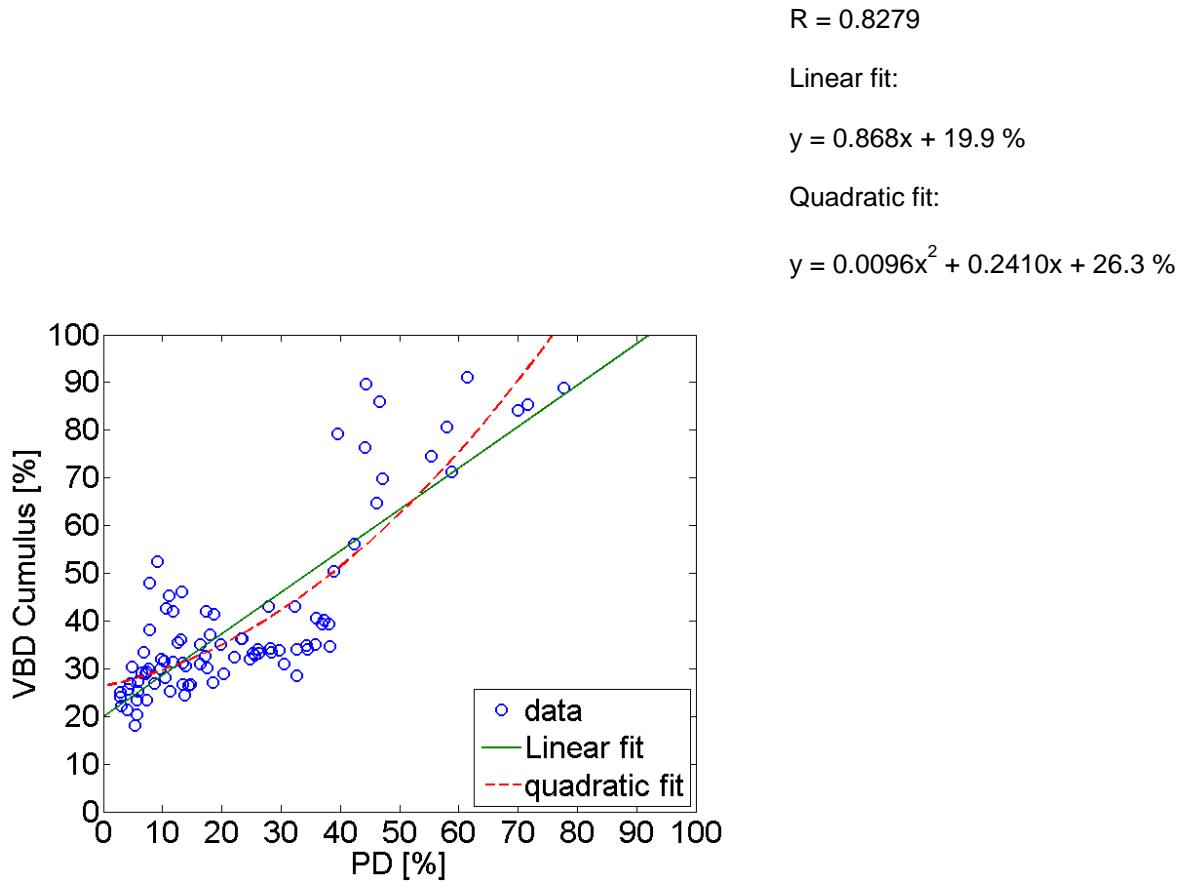


Figure 3. CumulusV density measures compared with Cumulus 2D (area) method. There is not a marked difference between the new dataset and the prior.

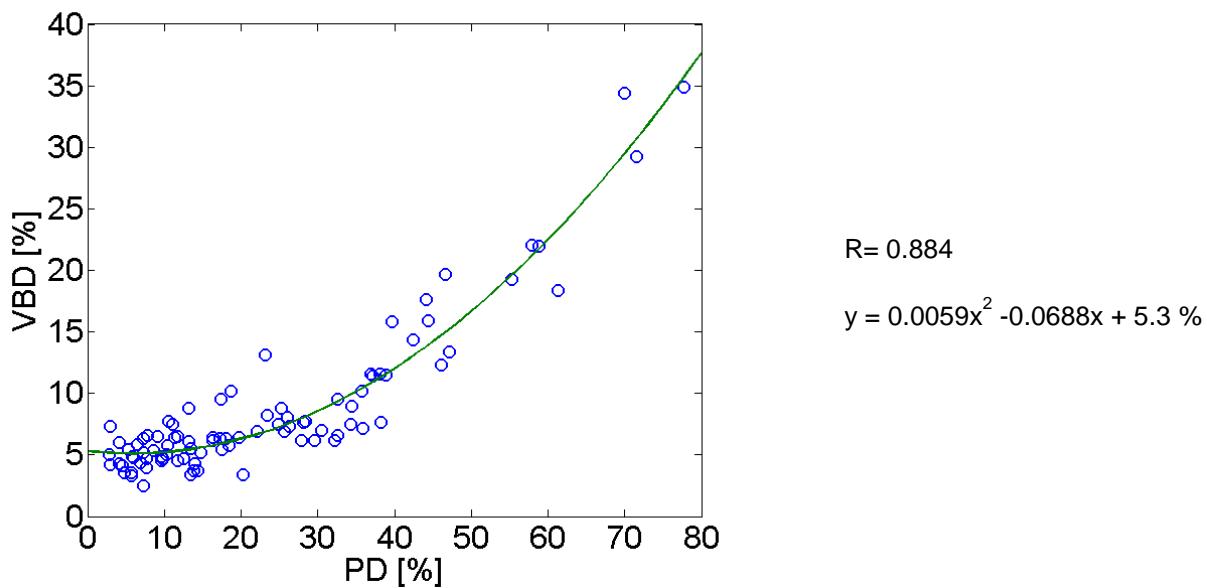


Figure 4. Volpara density measurements compared with Cumulus 2D (area). This method has strongest correlation with the area based method with an R value of 0.884.

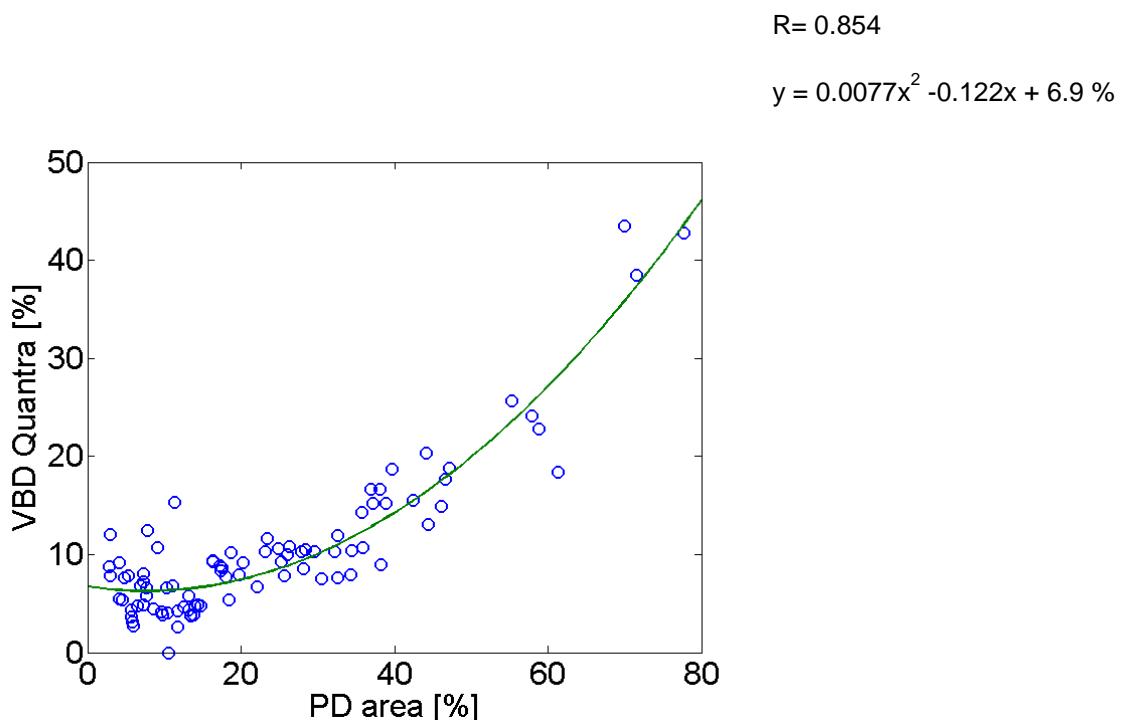


Figure 5. Quantra density measurement compared with Cumulus 2D (area). This method had good correlation with the area based measurement.

Tiled Images. The issue of how to address women with large breasts who have multiple images in the same projection (view) to cover the area of the breast was evaluated. We performed a retrospective study to evaluate this topic. The data was presented at the International Workshop for Mammography (IWDM) in Gifu, Japan, in July 2014. The paper was published in the conference proceedings. Here is the abstract:

Abstract. Tiled images are sometimes obtained for women with large breasts, which is a limitation of receptor size. In this retrospective HIPAA compliant study, automated breast density measurements for tiled images are compared with full MLO and CC views. Women with tiled views between July and December 2007 followed by full views within 15 months were included. Volumetric breast density (VBD) for tiled MLO views had very good correlation with full views ($r = 0.88$), while correlation between tiled and full CC views was poor ($r = 0.31$). VBD for all women requiring tiled CC views was low (<10%). In conclusion, VBD measured from a tiled MLO view is a reasonable substitute

for a full MLO measure. Attributable risk of breast density for women requiring tiled CC views may be sufficiently low compared other factors such as high body mass index

Task 5: Populate and validate database with existing data (months 3-6) HARVEY
Completed.

5a. Link existing radiology data sets with Clinical Data Repository (month 3-4). Our Breast Cancer Database is in Microsoft Access format. The entries, while clear to us, are variable in style. For example, the term half-sister may have been entered as "half-sister," "half sister," or "1/2 sister." These variables reduce the accuracy of prepopulation of the study database very challenging and with many errors. Because of this, we used this database and Epic (our institutional electronic medical record) to manually obtain information about our case patients prior to their arrival to clinic that can be used to help patients complete the form. In addition, information about breast cancer diagnosis, including histologic type, grade, stage, was obtained from our Breast Cancer Database and Epic.

5b. Identify missing data that can be obtained via chart review (month 3-4). This was an ongoing process as cancer case patients completed their survey. For case patients that were no longer in the area or have passed away, we populated the information using both the MS Access database and Epic.

5c. Conduct chart review for selected cases (month 4-6). Comparison of information from the Breast Cancer Database and medical records showed good consistency (for example, details of treatment for cancer cases were the same between sources).

Task 6: Case ascertainment (month 6) KNAUS

6a. Apply inclusion/exclusion criteria to populated database (month 6).

6b. Date of diagnosis and age identification for matching with controls (month 6).

6c. Identify specific missing data fields that can be obtained by interview (month 6).

Completed. Case ascertainment was performed using a combination of our Clinical Data Repository and our MS Access Database. Over 2000 eligible cases were identified.

Task 7: Control ascertainment (month 7) KNAUS

7a. Apply inclusion/exclusion criteria to potential controls (month 7)

7b. Match to cases within five years of diagnosis of breast cancer (month 7).

7c. Identify up to 15 potential controls for each case (month 7)

Completed. Over 28,000 potential control patients were identified. The cases and potential controls were contained in a MS Excel spreadsheet so that when patients presented to the clinic, the research staff could easily see if she qualified for the study.

Task 8: Develop Automated 2D Cumulus program (months 7-12) YAFFE

8a. Create a volumetric composition map using 3D Cumulus on Dr. Harvey's previously validated 340 mammogram dataset (months 7-9)

8b. Perform quasi-2D density analysis on dataset maps (month 10).

8c. Optimize algorithm during Dr. Harvey's visit to Toronto (month 11)

Completed. The current 2D method of Cumulus has a well validated association with breast

cancer risk. However this method is labor intensive and used only in research. Because 2D methods of measuring breast density are not dependent upon having accurate measurements of breast thickness, an automated 2D Cumulus measurement may prove more reliable than 3D methods. Dr. Yaffe's group has developed an automated 2D method. Figure 7 shows the automated 2D (area) results on the same dataset presented in Task 4 (figures 1 and 2). The same limitation, the age of the mammograms, applies here. The correlation between the automatic area and the cumulus area is similar to that seen in Figure 1. However, the relation between the area measurements is linear, compared to the quadratic relation between Cumulus volume and Cumulus area. The value of $R = .88$ is actually better than is found in tests of inter-observer variability with well trained readers.

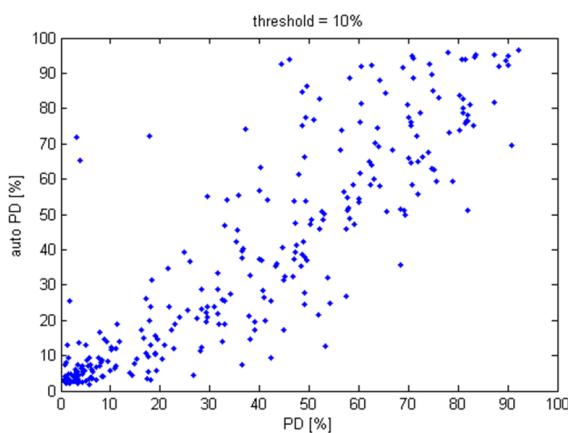


Figure 7: Comparison between the PD (percent density using Cumulus area) and the automatic PD. The correlation is $R=0.88$ and the linear least square fit between the two PD measurements is $y=0.97x+2.2\%$,

Task 9: Evaluate precision of 3D Cumulus method (months 7-12) HARVEY

9a. Develop IRB protocol and obtain approval (months 7-8)

Completed. Precision reflects the consistency of a repeated measurement. It does not necessarily reflect the accuracy or validity of the measurement. Precision is important however to the model since changes in breast density will translate to changes in breast cancer risk. Therefore, noise in measurement should be minimal.

Thirty women were recruited under this protocol, which was approved by the UVa IRB and the CDMRP. All women presented for screening mammography. Each patient underwent the standard of practice 4-view mammogram. Following this, a different technologist obtained a second craniocaudal image of the left breast. Density analysis of these 30 paired images was performed to assess the precision, or accuracy of a repeated measure. The paired images were analyzed using Cumulus 2D manually performed by Dr. Harvey and three automated volumetric methods using CumulusV, Volpara, and Quantra. The precision was excellent for all methods but best results were obtained using Volpara.

The manuscript was prepared, submitted, and accepted for publication by the journal *Radiology*. The abstract is below.

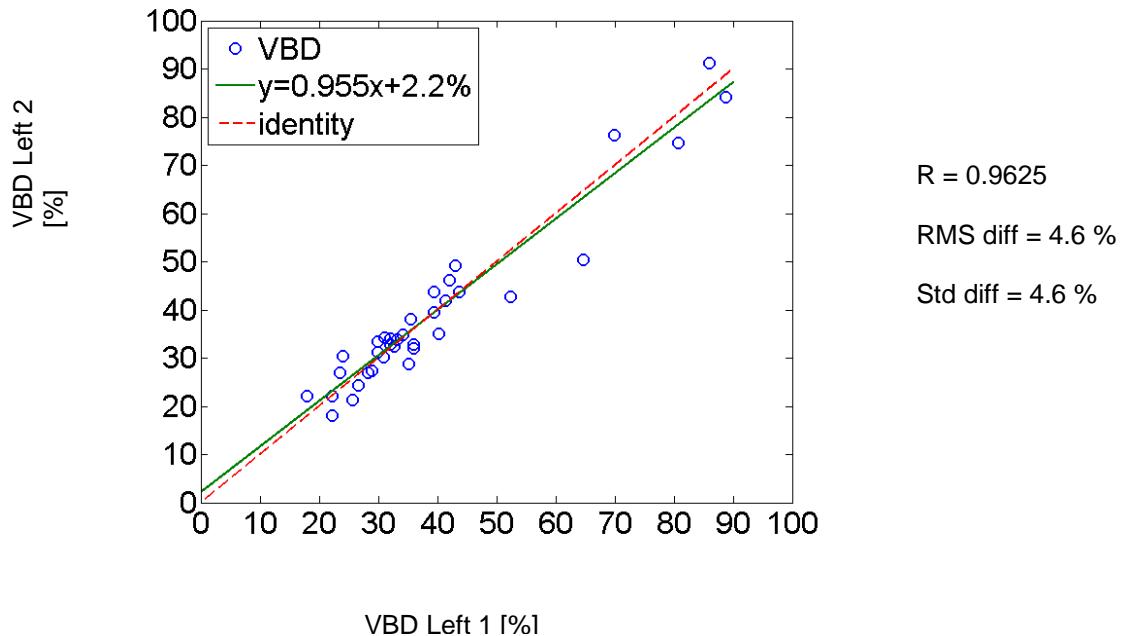


Figure 8. Precision of CumulusV. Excellent precision is present using this method with an R value of 0.96.

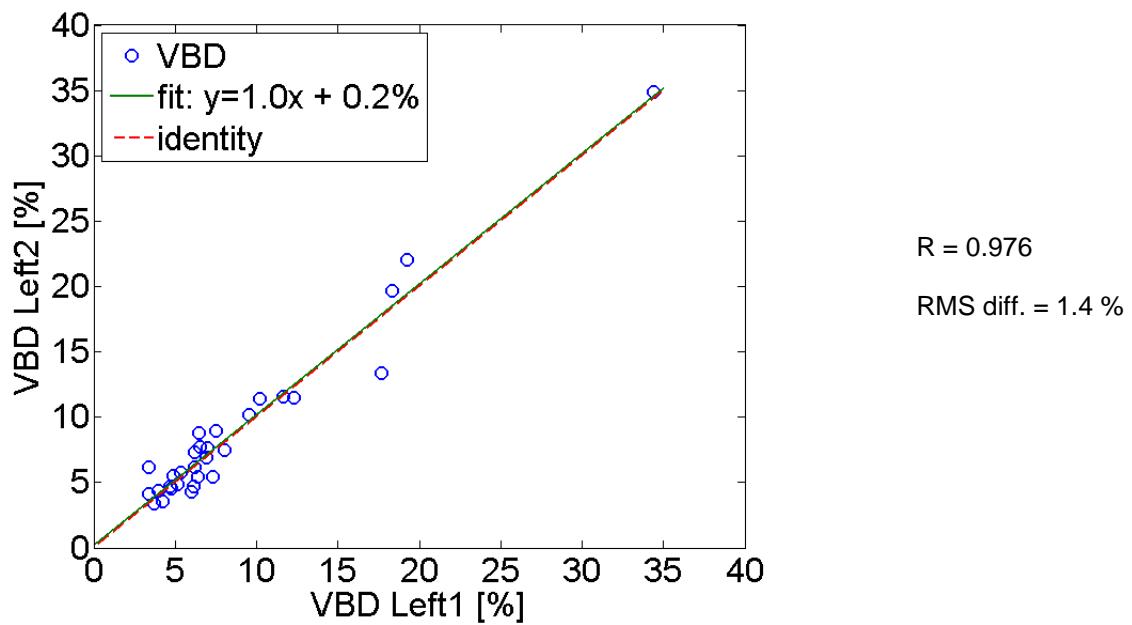


Figure 9. Precision using Volpara density measurement. Precision is similarly very high with an R value of 0.976.

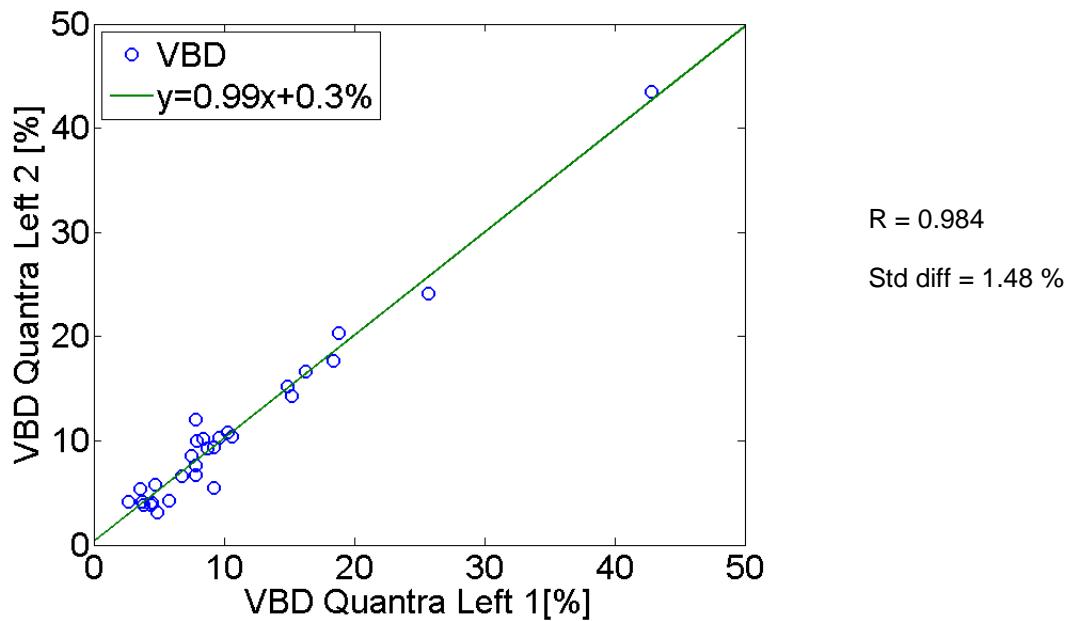


Figure 10. Precision using Quantra density measurement. Also excellent precision with R value of 0.984.

Background: Automated measures of breast density must have low variability to be useful in a breast cancer risk model. A small change in density could imply considerable differences in risk.

Methods: Thirty women undergoing screening mammography were recruited to undergo a repeated left craniocaudal view by a second technologist in this prospective, IRB-approved, HIPAA compliant study. Breast density was measured using an area method (Cumulus ABD) and three automated volumetric methods (CumulusV, Volpara, Quantra). Discrepancy was obtained for each algorithm by subtracting the second from the first measurement (Δ_{1-2}).

Results: Variability was higher for Cumulus ABD and CumulusV compared with Volpara or Quantra. The *within-breast* density measurement standard deviations were 3.32% (95% CI 2.65, 4.44%), 3.59% (95% CI 2.86, 4.48%), 0.99% (95% CI 0.79, 1.33%) and 1.04% (95% CI 0.82, 1.39%) for Cumulus ABD, CumulusV, Volpara, and Quantra, respectively. Although, the mean discrepancy between the repeat breast density measurements was not statistically different from zero for any of the four algorithms, larger absolute breast density discrepancy (Δ_{1-2}) values were associated with larger breast density values for Cumulus ABD and CumulusV, but not for Volpara and Quantra.

Conclusion. The variability in a repeated measurement of breast density is lowest for Volpara and Quantra; these algorithms may be more suited to incorporation into a risk model.

Task 10: Case enrollment (months 7-24) KNAUS

Task 11: Control enrollment (months 8-24) HARVEY

Completed. After building the dataset, iPads were programmed for survey data acquisition by the patient. This was a very efficient, secure system to administer the survey. The data was uploaded

to the secure server immediately, and the data removed from the iPad after completion. A token system was set up for patient anonymity. Patients could also access the survey from home using their token.

Study recruitment was completed on December 31, 2013. A total of 825 cases and 2598 control patients were enrolled for a total of 3423. The characteristics of the case and control population are relatively similar (Table 1).

Table 1. Characteristics of the Study Population

Variable	Cases – Survivors	Controls
Age	62.6 years (SD = 11.5)	61.2 years (SD = 9.7)
Race	83.6% White; 15.2% Black	88.2% White; 11.1% Black
Height	64.2 inches (SD = 2.7)	64.2 inches (SD = 2.9)
Weight	170.1 pounds (SD = 41.1)	160.2 pounds (SD = 36.9)
Educational level	25.7% graduate degree; 18.9% college degree; 25.3% some college; 19.1% high school	29.0% graduate degree; 25.1% college degree; 20.2% some college; 14.9% high school

All study images were collected and density analyzed using CumulusV, Quantra, and Volpara.

As part of the study, we also requested an optional donation of a blood sample from patients. The blood sample process was set up after recruitment was underway. We obtained 1297 blood samples (166 cases, 1091 controls). These banked samples are stored in a minus 80 degree Celsius freezer purchased through another grant. These may be helpful if serum hormone levels are needed to further refine the model.

Task 12: Establish accuracy of 3D Cumulus using different machines (months 13-18) YAFFE
Completed. In order to determine whether the density measurements of mammograms performed on machines from different vendors have significantly different results, and if a “machine type” variable is necessary in the model to control for the variability, a study was performed.

The new dataset used in Task 4 was also used for this task. All women in this dataset had both GE and Hologic mammograms within 15 months. There were 65 patients that qualified for this study.

$$Y = 0.55x + 10\%$$

$$R^2 = 0.55$$

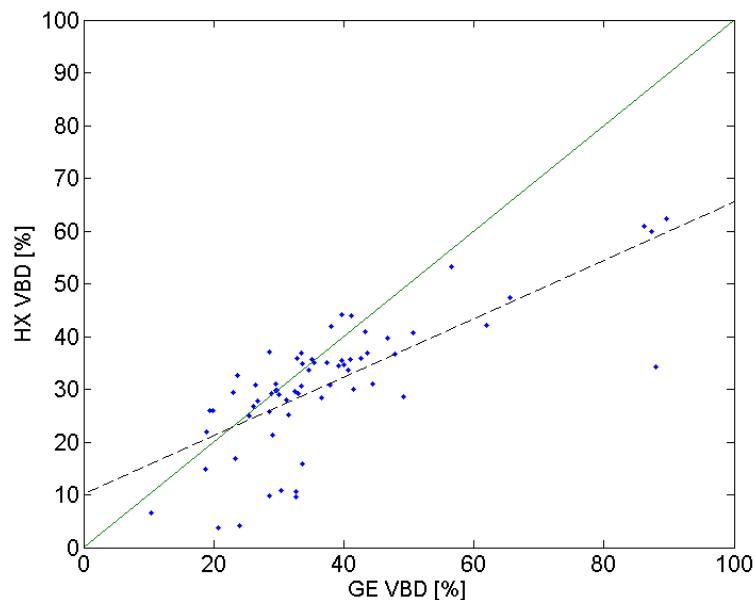


Figure 11. Volumetric breast density (VBD) using CumulusV of mammograms obtained using GE and Hologic (HX) machines on the same patient within 15 months. There is moderate correlation. Density measures using images from Hologic machines are uniformly lower than GE.

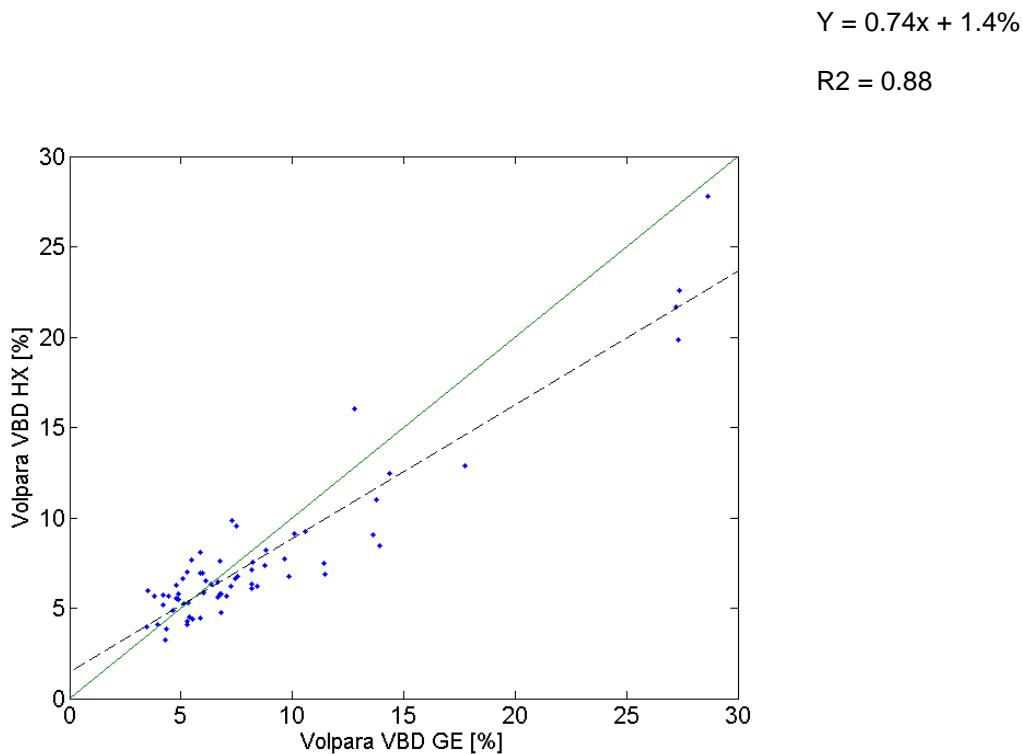


Figure 12. Volumetric breast density (VBD) using Volpara of mammograms obtained using GE and Hologic machines on the same patient within 15 months. There is improved correlation compared with CumulusV. Volpara is less dependent on accurate breast thickness readouts provided by the manufacturers.

Task 13: Finalize database for analysis (months 24-25) KNAUS
Completed in March 2014.

Task 14: Community engagement and publicity campaign (months 1-24) HARVEY
Completed

During the first few months of the study, we conducted two focus groups, which were very helpful. The project title developed for public use is: “The UVa Mammography Project: Shaping the Future of Breast Cancer Screening.” Our advocates were invaluable in this process.

We created a project website (<http://www.healthsystem.virginia.edu/pub/ct/ct15885>, live date July 2012). We did not use Twitter. However, Vernal Branch, one of our advocates, posted tweets about the project through the Virginia Breast Cancer Foundation.

The UVa Breast Program Facebook page went live in August 2012 (<https://www.facebook.com/uvabreastcare/timeline>) has 1838 “likes.” There are over 100 posts per year. At least 10 of these posts were specific to study questions- breast density

awareness, risk factors for breast cancer, etc, each study year.

A rack card and letter to potential case/control patients was developed to aid recruitment. We are very grateful to our advocates and focus groups for their hard work on these items.

Representatives from the project were present to provide information at the annual Charlottesville Four Miler Training Program and Charlottesville Womens Four Miler Race.

Task 15: Conduct focus groups (months 12-20) HARVEY

Completed

The Staff of the Center for Survey Research (CSR) conducted ***two initial focus groups*** in ***January 2012***. The results were very enlightening. The purpose was:

1. To understand what participants know about breast cancer screening and risk
2. To explore participants' reactions to information about breast density as a risk factor
3. To discuss the Harvey study and motivations for recruiting participants into the study
4. To discuss names for the study

The two focus groups were women without a personal history of breast cancer and women who were breast cancer survivors. The Non-Cancer Group met on January 17, 2012. Eleven participants were recruited who are patients of Dr. Harvey at the Northridge Office or referrals from the UVa Medical staff. The Survivors Group met on January 24, 2012. Nine participants were recruited who are members of a cancer support group coordinated by Diana Cole, at the Emily Couric Clinical Cancer Center, or referrals from Breast Surgery.

Agenda for the Focus Groups:

1. Discussed screening and how participants make decisions about screening
2. Kathy Repich presented Dr. Harvey's slides on risk factors and the existing models for measuring risk
3. Discussed participants' reactions to the presentation and their knowledge of the risk factors
4. Discussed recruitment for the study and what would motivate people to participate in the study
5. Presented ideas for naming the project and gave participants an opportunity to rate them and share others

The non-cancer focus group cited the following as motivating factors for participation in the study: convenience, legitimacy, importance, size of the study, self-education, learn about risk factor models, and altruism ("To help my daughter"). Cancer survivors cited the following as additional motivating factors for participation: to reduce false positives for others, altruism ("I had treatment options because of other trial participants") and "the idea that someday, there may be customized recommendations."

The results of the focus groups lead us to these considerations for messaging on recruitment materials: highlight convenience of participation, address patient privacy, highlight size / scope / potential impact of the study, assess effectiveness of giveaways as recruitment tool – non-cancer group not in favor public display of study participation, and altruism ("Your participation could

impact future generations.”). We subsequently decided not to give away study logo items (t-shirts, tote bags), but to thank participants with a thank you note highlighting their altruism. The note also includes a \$5 gas card as a token of appreciation.

Two additional focus groups were held in **January and February 2013**. The purpose was to vet the telephone survey instrument. One group was held in Charlottesville and was facilitated by study survivor Carolyn Achenbach. The second group was held in Richmond and facilitated by survivor, Vernal Branch. The groups were primary women without a breast cancer diagnosis but did include some survivors. The additional review was very helpful to address phrasing and to clarify end points.

Task 16. Conduct message testing telephone survey (months 12-20). Harvey

Completed. The telephone survey was developed with the UVa Center for Survey Research based on women’s responses to the second set of focus groups. Our advocates were very helpful in the development and review of the survey.

The goals of the survey were:

- Assess Virginia women’s current knowledge about cancer screening recommendations and breast density
- Evaluate willingness of women to change their breast cancer screening practices based on new recommendations
- Identify characteristics of women who are willing and unwilling to change their screening practices
- Inform design of future educational campaigns to promote new tailored recommendations

The survey used a triple frame scientific random sample that include listed landline phone numbers (random from phone directory), landline RDD-Random Digit Dialing (includes unlisted phone numbers), and cell phone numbers (RDD from cell phone exchanges at Virginia billing centers).

The survey topics included:

- Demographics
- Personal history
- Current breast cancer screening practices
- Risk perception
- Understanding of breast density
- Understanding of current guidelines
- Willingness to change screening practices
- Information sources

The results were analyzed. The following abstract was presented at the American Association for Public Health:

What do women know about breast density?
RESULTS FROM A POPULATION SURVEY OF VIRGINIA WOMEN

Breast density reduces the sensitivity of mammography and is a moderate independent breast cancer risk factor. Virginia is one of fourteen states that currently require

providers to notify patients when they have dense breasts. However, little is known about what women in the general population know and understand about breast density. This survey study assessed knowledge about breast density, its impact on mammography and its relationship to breast cancer risk. A random sample of 1,024 Virginia women between age 35-70 years and without breast cancer, reached by landline and cell phone, completed a 24-minute interview. Thirty-six percent of respondents had been informed about their breast density by a doctor. Few respondents (5.3%) were able to answer all three breast density knowledge questions correctly. Women with a higher perceived risk of breast cancer, familiarity with its risk factors, or familiarity with current recommendations for screening were more likely to have accurate breast density knowledge; those in rural regions were less likely. Seventy-five percent of respondents reported being either somewhat or very familiar with risk factors for breast cancer, but less than 1% proved able to list breast density as a risk factor. These results suggest that while women are becoming aware of the term “breast density”, they may not understand its relationship to cancer detection by mammography and, especially, its relation to breast cancer risk. Improved public health education about breast density is necessary to augment new legislation to help women evaluate and manage their breast cancer risk.

The following abstract regarding women’s willingness to change screening behaviors was presented at the American Society of Preventive Oncology:

Are Women willing to change Breast Cancer Screening Guidelines?

Purpose: In 2009, the US Preventative Task Force released new guidelines for screening mammography that sparked both public and professional controversy. While the guidelines are evidence based, they are not personalized to a woman’s individual risk factors. This interview study was designed to evaluate the willingness of women to change their breast cancer screening practices based on new personalized recommendations.

Materials and Methods: A random sample of 1,024 Virginia women between age 35-70 years and without breast cancer, reached by landline and cell phone, completed a 24-minute interview.

Results: Just over half (54.6%) of women are definitely or probably willing to reduce their frequency of breast cancer screening compared to 81.9% who are definitely or probably willing to increase screening. The most cited disadvantage for reduced screening was delayed detection of breast cancer (77%) while the most cited advantage for increased screening is earlier detection (82%). Women are willing to change their type of screening (92.3%). Women who were more likely to be willing to reduce screening are those with a lower perceived risk of breast cancer, less familiarity with risk factors and recommendations. When asked what they needed to know to make a change, women cited advice of a doctor (52.1%), research/evidence (38.9%) and comparison with old recommendations (22.5%) most frequently. Advice of a radiologist was only stated by 2.3% of the women.

Conclusion: These results suggest that most women will be willing to change their breast cancer screening frequency especially if recommended by their primary care physician. Women do not view their radiologist as having a primary role in delivering screening recommendations; this underscores the need to educate primary healthcare providers regarding breast screening recommendations.

Task 17. Model Development (Months 24-36) KNAUS

a. Initial Model Development.

The database was closed in May 2014, following completion and cleaning of data. Analysis has been performed.

Controls were matched to cases in a 2:1 ratio based on age group, race, and education, using the GREEDY algorithm. Case-control selections were made using the weighted sum of the absolute differences between the case and control matching factors. Conditional logistic regression using the partial likelihood function from Cox proportional hazard's regression was used to fit risk prediction equations to the matched case-control study dataset, with stratification for each case matched set.

A full model was estimated including all available covariates for use as a model performance reference standard. Reduced Models were then estimated including covariates in the full model that had a Wald Chi-Square/degrees of freedom ratio > 1.0 (A) and then again including covariates with p value < 0.10 (B). A Minimal Model was then estimated including covariates from Model B with Wald/Chi-square/DF > 5.0 . The performance of the full, reduced, and minimal models was measured using the C index and the maximum R-Square statistic.

Multivariable analysis was conducted using 860 cases and 1,683 controls with 1 or more breast studies reported for the surveyed population. The matching process yielded balanced matching factor values between cases and controls, with no significant differences in age group ($p = 0.95$), race ($p = 0.13$), or education ($p = 0.86$).

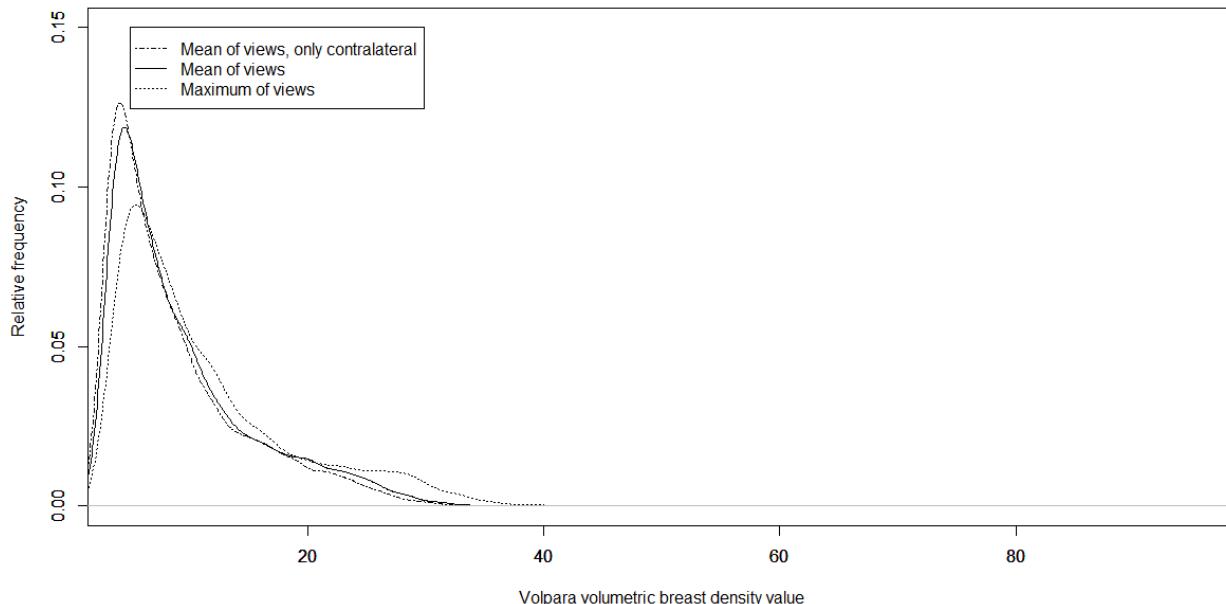


Figure 13. Distribution of Volpara densities.

The results of the preliminary model were presented at the San Antonio Breast Cancer

Symposium in December, 2014.

Table 2. Model Development Results

Model Development Results			
Model	Number of Covariates	Maximum Adjusted R ²	C Statistic
Full Model (All available covariates)	62	0.62	0.86
Reduced Model A: (Full Model with Wald Chi-Square/DF > 1.0)	34	0.59	0.85
Reduced Model B: (Reduced A with Wald Chi-Square p value < 0.10)	21	0.56	0.84
Minimal Model: (Reduced Model B covariates with Wald Chi-Square/DF > 5.0)	13	0.54	0.82

The addition of volumetric breast density improved breast cancer risk discrimination. Our model uses an automated measurement of breast density used as a continuous variable that proved to be one of the top five predictors of breast cancer risk in our population. Discrimination is key in model development if screening recommendations are to be individualized. Even the minimal model that includes only 13 covariates demonstrates improved discrimination (0.82) compared with the Tyrer-Cuzick (IBIS) model (0.74).

In evaluating data, it became apparent that the referral pattern to UVa influenced our study population. For example, smoking and parity were strong risk factors for breast cancer; smoking is either mildly protective or not a breast cancer risk factor and parity is protective. Corrections were made to adjust for financial status (insurance, financial need, etc) and region. Once this was performed, known risk factors performed correctly.

We have been working with Dr. Jack Cuzick in the UK (Barts and London), who developed the

Tyrrer-Cuzick Model. Since this model has the highest overall performance, we have calculated performance of the TC Model in our study population and evaluated the addition of volumetric density (Volpara) in risk prediction. We are working on a paper draft with the goal of submitting in February 2016.

b. Evaluate normal temporal changes of breast density.

In progress. Our priority is to publish results of the relationship of volumetric breast density to risk and of the breast cancer risk model.

c. Evaluate best breast density measurement associated with breast cancer risk.

The above analysis in A was performed using Volpara. The C-statistic for CumulusV was not statistically significant, while the results for Quantra were significant but not as strong.

d. Develop plan for external validation of the model.

We have identified 5 sites in addition to UVa that currently prospectively collect demographic and breast cancer risk data as part of their clinical practice. Four sites have long term archives of raw (“for processing”) mammograms and two are initiating. The next steps will be to assess risk factors collected, format of data, ensure and validate data extraction from archives.

Site	Prospective Data Collection System	For Processing Mammograms	Number of Sites	Screening Volume per Year
University of Virginia	MagView	Yes, > 10 years	3	15,000
Emory University	MagView	Yes, > 5 years	5	60,000
Staten Island Hospital	MagView	Yes, > 10 years	1	30,000
Wendi Logan Breast Center, Rochester NY	Internal System	Yes, >10 years	1	50,000
University of Texas, Southwestern, Dallas TX	MagView	Initiating December 2015	2	30,000
MD Anderson and Herman Health System, Houston TX	PenRad	Initiating January 2015	10	100,000

4. KEY RESEARCH ACCOMPLISHMENTS:

- Performed outlier correction for area versus CumulusV and Volpara density measurement software programs. The quadratic correlation with manual area density

measurement for corrected CumulusV is $R= 0.87$. Second dataset showed R values of 0.84 for CumulusV, 0.88 for Volpara, and 0.85 for Quantra.

- Study of patients with tiled images also performed with results presented at the International Workshop on Breast Imaging in Gifu, Japan, 2014, and published in the conference proceedings.
- Developed Automated Cumulus2D software program and compared with manual area density measurements; $R=0.88$.
- Precision study completed. The Rvalues for repeated left craniocaudal mammogram images are 0.96 for Cumulus, 0.98 for Volpara, and 0.98 for Quantra. Published in *Radiology*.
- Evaluated differences in density measures between mammography machine vendors. Density measurements from Hologic machines are uniformly lower than from GE images when using CumulusV ($R= 0.55$). However, the relationship is more linear and consistent when using Volpara ($R = 0.88$).
- Survey of 1024 Virginian women with results demonstrating low knowledge of breast density as a risk factor and that women will rely on their primary health care providers for advice regarding screening strategies. This will require education of health care providers regarding knowledge of breast density moving forward.
- Produced initial breast cancer risk model using Volpara automated software density program. The C-statistic of 0.86 for the full model with a minor decrease to 0.82 with the reduced model. Breast density was one of the top 5 risk factors in the model. This is considerably higher than the C-statistic of the comprehensive Tyrer-Cuzick risk model, of 0.74.
- Substudy to evaluate accuracy of volumetric methods of measuring density compared with breast MRI performed (submitted to *Radiology*).
- Substudy of case patients showed no change in re-excision rates for women with dense breast tissue (presented at San Antonio Breast Cancer Symposium, in press).
- Substudy of case patients showed increased association of HER-2 positive cancers for women with dense breasts using Volpara, but not BI-RADS density descriptors (presented at San Antonio Breast Cancer Symposium, in draft).
- Identified five clinical sites in addition to UVa that prospectively collect risk data that can be used to validate our model. Assessment of risk data and data extraction will be performed to assess logistics of model validation.

5. CONCLUSION:

Much of the work of this project was related to evaluating volumetric measures of breast density and their relationship to breast cancer risk. Our work has shown that the Volpara algorithm (compared with CumulusV and Quantra) requires less outlier correction, has better reliability (precision), and is more uniform between mammography machine vendors. It also has excellent correlation with breast MRI confirming accurate measurements. Volpara density also had the highest association with breast cancer risk. Moving forward, the Volpara algorithm appears to be the most useful in automated assessments of breast density.

Interestingly, Breast Density Notification Laws have been passed in 23 states since this grant was awarded in 2011. Virginia was the third state to have a density notification law, which went into effect in 2012. Although 36% of Virginian women surveyed had been informed of

their breast density, less than 1% cited density as a risk factor for breast cancer. Clearly, additional education needs to be performed.

Our initial model shows that the addition of volumetric breast density (using Volpara algorithm) results in significant improvement in breast cancer risk prediction. Because of UVa referral patterns (serving a large indigent population), adjustments for financial need and region were necessary. We are currently working with Professor Jack Cuzick, an international leader in breast cancer risk modeling and developer of the Tyrer-Cuzick Model, in data analysis. Our results are in draft format with submission planned in February 2016.

Validation of our modeling is required to best understand risk prediction. To this end, we have identified five sites that have prospectively collected risk data and archive digital mammograms to perform density analysis. These sites together perform ~270,000 screening mammograms per year, which translates to ~1350 new breast cancer cases per year. As there is prospective collection of risk and density data, we will be able to assess risk prediction and make needed corrections for race/ethnicity in this highly diverse group.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

Lay Press Articles:

1. One Voice. Virginia Breast Cancer Foundation, Winter Spring issue.
2. UVa Alumni News. Fall 2015. Article about the Building a Better Model Project.
3. Numerous FaceBook posts about the Project on the UVa Breast Care Program page. Example in Appendix.

Peer Reviewed Scientific Articles:

1. J Harvey, O Alonzo, G Mawdsley, T Ashlafeiy, R Highnam, M Yaffe. Managing Tiled Images in Breast Density Measurements. Proceedings of the 12th International Workshop on Breast Imaging (IWDM), Gifu, Japan, 2014.
2. Alonzo-Proulx O, Mawdsley GE, Patrie JT, Yaffe MJ, Harvey JA*. Reliability of Automated Breast Density Measures. Radiology 2015; 275:366-376.
<http://dx.doi.org/10.1148/radiol.15141686>
3. Edwards BL, Guidry C, Larson K, Harvey JA, Cohn WF, Novicoff W, Schroen AT. “Does Mammographic Density Impact the Margin Re-excision Rate after Breast Conserving Surgery?” Annals of Surgical Oncology (accepted, in press).
4. Guterbock T, Cohn W, Novicoff W, Eggleston C, Knaus W, Yaffe M, **Harvey J.** What Do Women Know About Breast Density? Cancer, Epidemiology, Biomarkers & Prevention (submitted).

Abstracts:

1. “Managing Tiled Images in Breast Density Measurements”
J Harvey, O Alonzo, G Mawdsley, T Ashlafeiy, R Highnam, M Yaffe
12th International Workshop on Breast Imaging (IWDM)
Gifu, Japan, June 29-July 2, 2014
2. “What do Women Know About Breast Density?”

Gutterbock TM, Rexrode DL, Eggleston C, Cohn WF, Novicoff W, Knaus WA, Harvey JA
 142nd meeting of the American Public Health Association
 New Orleans, Louisiana, November 15-19, 2014

- 3. "Got Patient Advocates? The value of patient advocate participation in a large research study to develop personalized risk-based breast cancer screening strategies."
 V Branch, C Achenbach, KG Ross, WF Cohn, MD Yaffe, WA Knaus, JA Harvey.
 37th Annual San Antonio Breast Cancer Symposium
 San Antonio, Texas
 December 9-13, 2014
- 4. "Association of Mammographic Density and Molecular Breast Cancer Subtype"
 BL Edwards, KA Atkins, GJ Stukenborg, WM Novicoff, KN Larson, WF Cohn, JA Harvey, AT Schroen.
 37th Annual San Antonio Breast Cancer Symposium
 San Antonio, Texas
 December 9-13, 2014
- 5. "Volumetric breast density improves breast cancer risk prediction"
 JA Harvey, G Stukenborg, WF Cohn, K Repich, W Novicoff, O Alonzo, MD Yaffe, WA Knaus
 37th Annual San Antonio Breast Cancer Symposium
 San Antonio, Texas
 December 9-13, 2014
- 6. "Does Mammographic Density Impact the Rate of Margin Re-excision after Breast Conserving Surgery?"
 Edwards B, Guidry C, Larson K, Novicoff W, Harvey JA, Schroen AT
 15th Annual Meeting, American Society of Breast Surgeons
 Las Vegas, Nevada
 April 30-May 4, 2014
- 7. "What Do Women Know About Breast Density?"
 Guterbock T, Cohn W, Novicoff W, Eggleston C, Knaus W, Yaffe M, Harvey J
 142nd Annual Meeting, American Public Health Association
 New Orleans, Louisiana
 November 15-19, 2014
- 8. "Are Women Willing to Change Breast Cancer Screening Guidelines?"
 Cohn W, Novicoff W, Dean McKinney M, Guterbock T, Rexrode D, Eggleston C, Harvey J, Knaus W
 39th Annual meeting, American Society of Preventive Oncology
 Birmingham, Alabama
 March 14-17, 2015

***Honorable Mention Award**

Presentations:

- 1. "Managing Tiled Images in Breast Density Measurements"
 J Harvey, O Alonzo, G Mawdsley, T Aslhafeiy, R Highnam, M Yaffe
 12th International Workshop on Breast Imaging (IWDM)
 Gifu, Japan, June 29-July 2, 2014

2. "What do Women Know About Breast Density?"
Gutterbock TM, Rexrode DL, Eggleston C, Cohn WF, Novicoff W, Knaus WA, Harvey JA
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3. "Got Patient Advocates? The value of patient advocate participation in a large research study to develop personalized risk-based breast cancer screening strategies."
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39th Annual meeting, American Society of Preventive Oncology
Birmingham, Alabama
March 14-17, 2015

***Honorable Mention Award**

7. INVENTIONS, PATENTS AND LICENSES: None

8. REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research. Reportable outcomes are defined as a research result that is or relates

to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. This list may include development of prototypes, computer programs and/or software (such as databases and animal models, etc.) or similar products that may be commercialized.

- Tiled images have little effect on density measurements since the vast majority are in women with fatty breasts and low percent density. Published in IWDM proceedings.
- Automated Cumulus2D software program developed with good correlation with manual approach. However, given high performance of Volpara algorithm, less likely to use alternative measures such as this one.
- High reliability of volumetric breast density algorithms- highest for Volpara. Demonstrates that this software can be reliably used to measure breast density. Published in *Radiology*.
- Demonstrated that density measures between mammography machine vendors are more linear and consistent when using Volpara than other algorithms due to lower reliance on compressed breast thickness accuracy. This is important since many machine types are used worldwide, and risk prediction should not vary by how a mammogram is obtained.
- Found that although 36% of Virginian women had been told their breast density by a healthcare provider, less than 1% cited density as a breast cancer risk factor.
- Produced initial breast cancer risk model using Volpara automated software density program. The C-statistic of 0.86 for the full model with a minor decrease to 0.82 with the reduced model. Breast density was one of the top 5 risk factors in the model. This is considerably higher than the C-statistic of the comprehensive Tyrer-Cuzick risk model, of 0.74.
- Percent breast density is highly correlative but slightly lower for Volpara compared with MRI. This is more apparent at higher breast density values (submitted to *Radiology*).
- No change in re-excision rates for women with dense breast tissue (in press).
- Demonstrated an increased association of HER-2 positive cancers for women with dense breasts using Volpara, but not BI-RADS density descriptors (in draft).
- A coalition of five clinical sites in addition to UVa has been formed that prospectively collect risk data and digital mammograms to obtain volumetric breast density. This coalition will be used to validate our model.

9. OTHER ACHIEVEMENTS:

Blood bank of study population patients that includes 1297 blood samples (166 cases, 1091 controls). These banked samples are frozen at -80C and can be used to assess the relative contribution of gene panels to risk assessment in our study population.

10. REFERENCES: None

11. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of

manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Appendix 1. Example Facebook Post

The screenshot shows a Facebook page for "UVA Breast Care". The left sidebar contains a post from a user named Betty Corrinne Hines Crusenberry, who has been a patient at UVA since 11 years old and now 51. She travel 5 hours each way to get her health in order. Below this is a section for users to share their thoughts, with a 5-star rating. The main feed shows a post from UVA Breast Care about a comprehensive breast cancer study. It includes a photo of a Christmas tree with ornaments and a link to a news article from NEWS-MEDICAL.NET. There are also posts from other local clinics like Jefferson Area CHIP and Pain Ends Here Clinic. A sponsored post from AARP Medicare Supplement is visible on the right.

Appendix 2. Abstracts not included in body of report

- Presented at San Antonio Breast Cancer Symposium, December 2014



Volumetric Breast Density Improves Breast Cancer Risk Prediction

JA Harvey, G Stukemborg, WF Cohn, K Repich, W Novicoff, O Alonzo, MD Yaffe, WA Knaus

P6-09-04



Background:

There is increasing interest in implementing personalized breast cancer screening strategies rather than relying on population based guidelines. Most risk models do not include breast density and two models that do rely on subjective BI-RADS categories; all have limited discriminatory ability (C-statistics ranging from 0.60-0.74). Our aim was to develop a model that includes an automated objective and numeric volumetric measurement of breast density combined with other known risk factors to improve risk prediction.

Methods:

This study was approved by our IRB and was HIPAA compliant. A case-control study design was used to evaluate the association between risk factors and breast cancer diagnosis. All women diagnosed with breast cancer during 2003-13 with a digital contralateral mammogram at the University of Virginia at the time of diagnosis were eligible as cases. All women without a breast cancer diagnosis but with a digital mammogram at UVA during 2003-2008 were eligible as controls. Risk factor information was collected using a self-reported electronic questionnaire. Mean automated volumetric breast density (Volpara, NZ) was calculated for each patient as a percentage. Controls were matched to cases in a 2:1 ratio based on age group, race, and education, using the GREEDY algorithm. Case-control selections were made using the weighted sum of the absolute differences between the case and control matching factors. Conditional logistic regression using the partial likelihood function from Cox proportional hazard's regression was used to fit risk prediction equations to the matched case-control study dataset, with stratification for each case matched set.

A full model was estimated including all available covariates for use as a model performance reference standard. Reduced Models were then estimated including covariates in the full model that had a Wald Chi-Square/degrees of freedom ratio > 1.0 (A) and then again including covariates with p value < 0.10 (B). A Minimal Model was then estimated including covariates from Model B with Wald Chi-square/DF > 5.0. The performance of the full, reduced, and minimal models was measured using the C index and the maximum R-Square statistic.

Results:

The study enrolled 3,445 women; 839 cases and 2,606 controls. Multivariable analysis was conducted using 860 cases and 1,683 controls with 1 or more breast studies reported for the surveyed population. The matching process yielded balanced matching factor values between cases and controls, with no significant differences in age group ($p = 0.95$), race ($p = 0.13$), or education ($p = 0.86$).

Model Development Results

Model	Number of Covariates	Maximum Adjusted R ²	C Statistic
Full Model (All available covariates)	62	0.62	0.86
Reduced Model A: (Full Model with Wald Chi-Square/DF > 1.0)	34	0.59	0.85
Reduced Model B: (Reduced A with Wald Chi-Square p value < 0.10)	21	0.56	0.84
Minimal Model: (Reduced Model B covariates with Wald Chi-Square/DF > 5.0)	13	0.54	0.82

The full prediction model (with 97df) yielded a C index of 0.86, and an R-Square of 0.62. The reduced model (with 15 df) had a C index of 0.83 and an R-Square of 0.54. Variables in the reduced model included: mean breast density; biopsy showing ADH, ALH/CIS; BMI; use of HRT, contraceptives, NSAIDS; smoking; exercise; parity; diabetes; family history of breast cancer; HBOC, Li-Fraumeni or Cowden Syndromes and/or BRCA mutation. Mean volumetric breast density was a leading independent predictor of case status in the full ($p<0.0001$), reduced models (A: $p=0.0212$, B: $p=0.0011$), and minimal model ($p=0.0048$).

Discussion:

The addition of volumetric breast density improved breast cancer risk discrimination. Our model uses an automated measurement of breast density used as a continuous variable that proved to be one of the top five predictors of breast cancer risk in our population. Discrimination is key in model development if screening recommendations are to be individualized. Even the minimal model that includes only 13 covariates demonstrates improved discrimination (0.82) compared with the Tyer-Cuzick (IBIS) model (0.74).

This study was supported by CDMRP BC100474

2. Presented at San Antonio Breast Cancer Symposium, December 2014: Got Patient Advocates? The Value of Patient Advocate Participation in a Large Research Study to Develop Personalized Risk-Based Breast Cancer Screening Strategies

Background: Over the last several years there has been confusion among women about breast cancer screening and patient advocates are increasingly used to help women understand the changes. In 2009, the U.S. Preventive Task Force (USPSTF) recommended that women under the age of 50 do not need routine screening. New state laws require breast density results to be given to women and their providers for making their screening choices. Women are not sure what to do with this information and are offered little guidance to personalize their screening recommendations. The goal of this study is to develop a risk model for improved personalized breast cancer screening recommendations. Patient advocates were incorporated throughout the design, recruitment, analysis, and dissemination phases of the study.

Methods: The research team included three patient advocates who participated as full members in the bi-weekly and quarterly team meetings throughout the duration of the study. All advocates were breast cancer survivors. The primary components of the study included focus groups to understand women's knowledge and views on breast density as well as personalized screening, a telephone survey to gain a broader view on these topics, and recruitment to a case:control study to build a breast cancer risk model that incorporates an automated measure of breast density.

Results:

Enrollment was completed over one year with 3,445 women; 839 cases and 2,606 controls. Study design and resulting recruitment strategies were reviewed early with regular feedback by the patient advocates. At the advice of the advocates, Facebook was chosen as primary social media, resulting in nearly 200 posts (stories) and 1583 likes for the project. Many of the posts were generated by or featured advocates. Regarding the focus groups, the advocates developed the questions. Women were informed about the study by the advocates and educated about breast density. The advocates were key in using the focus groups to find the right language for enrollment materials, obtain their perception of the importance of the study, and understand their

views regarding a new model for personalized screening for women. The advocates were likewise key in developing questions for and analyzing results of the telephone survey. In the analysis phase, the advocates assisted the team in understanding the results of the risk questionnaires. For example, most women did not know the type of breast cancer that they had been diagnosed with or even if it was invasive. The advocates confirmed how and why even highly educated women would not necessarily retain this information. Finally, the advocates will have a strong role in the eventual dissemination of the study findings to women.

Conclusions: The investigators have developed a breast cancer risk model that includes an automated measurement of breast density, with the goal of personalizing screening for women. The inclusion of patient advocates throughout all phases of the study improved knowledge and insight of the investigating team. Their role extended beyond community engagement and development of study materials. The advocates became integral members of the study team.

3. Presented at the 39th Annual meeting, American Society of Preventive Oncology, March 2015:

The screenshot shows the homepage of the *Cancer Epidemiology, Biomarkers & Prevention* journal. At the top, there is a navigation bar with links to Home, OnlineFirst, Current Issue, Past Issues, Subscriptions, Alerts, Feedback, AACR Publications, CME, and AACR Home. Below the navigation bar, it says "Institution: UNIV OF VIRGINIA". On the left, there is a large article thumbnail with the title "Are Women Willing to Change Breast Cancer Screening Guidelines?". The article summary, authors (W Cohn, W Novicoff, McKinney M Dean, T Guterbock, D Rexrode, C Eggleston, J Harvey, and W Knaus), and abstract are visible. The abstract discusses the willingness of women to change breast cancer screening practices based on personalized recommendations. To the right of the article, there is a sidebar with a login form for User Name and Password, and a "LOG-IN" button. Below the login, there are search fields for "Search CEBP" and "Advanced Search". Further down, there is a "Current Issue" section for December 2015, 24 (12) with a thumbnail image of the journal cover. A sidebar on the right lists various journal sections: About the Journal, Instructions for Authors/Editorial Policies, Submit a Manuscript, Author Services Center, Editorial Board, Information for Subscribers, Information for Reviewers, Information for Librarians, Information for Advertisers, Permissions & Reprints, and E-mail Alerts & RSS Feeds. The AACR logo is also present at the bottom of the sidebar.

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Reliability of Automated Breast Density Measurements¹

Olivier Alonzo-Proulx, PhD
Gordon E. Mawdsley, PhD
James T. Patrie, MS
Martin J. Yaffe, PhD
Jennifer A. Harvey, MD

Purpose:

To estimate the reliability of a reference standard two-dimensional area-based method and three automated volumetric breast density measurements by using repeated measures.

Materials and Methods:

Thirty women undergoing screening mammography consented to undergo a repeated left craniocaudal examination performed by a second technologist in this prospective institutional review board-approved HIPAA-compliant study. Breast density was measured by using an area-based method (Cumulus ABD) and three automated volumetric methods (CumulusV [University of Toronto], Volpara [version 1.4.5; Volpara Solutions, Wellington, New Zealand], and Quantra [version 2.0; Hologic, Danbury, Conn]). Discrepancy between the first and second breast density measurements (Δ_{1-2}) was obtained for each algorithm by subtracting the second measurement from the first. The Δ_{1-2} values of each algorithm were then analyzed with a random-effects model to derive Bland-Altman-type limits of measurement agreement.

Results:

Variability was higher for Cumulus ABD and CumulusV than for Volpara or Quantra. The within-breast density measurement standard deviations were 3.32% (95% confidence interval [CI]: 2.65, 4.44), 3.59% (95% CI: 2.86, 4.48), 0.99% (95% CI: 0.79, 1.33), and 1.64% (95% CI: 1.31, 1.39) for Cumulus ABD, CumulusV, Volpara, and Quantra, respectively. Although the mean discrepancy between repeat breast density measurements was not significantly different from zero for any of the algorithms, larger absolute breast density discrepancy (Δ_{1-2}) values were associated with larger breast density values for Cumulus ABD and CumulusV but not for Volpara and Quantra.

Conclusion:

Variability in a repeated measurement of breast density is lowest for Volpara and Quantra; these algorithms may be more suited to incorporation into a risk model.

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¹From the Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada (O.A., G.E.M., M.J.Y.); and Department of Public Health Sciences (J.T.P.) and Department of Radiology and Medical Imaging (J.A.H.), University of Virginia, Box 800170, Charlottesville, VA 22908. Received July 18, 2014; revision requested August 27; revision received November 13; accepted December 5; final version accepted December 18. Supported by the Congressionally Directed Medical Research Programs (grant BC100474). Address correspondence to J.A.H. (e-mail: jharvey@virginia.edu).

Breast density is an important breast cancer risk factor. Women with high mammographic breast density are about four times more likely to receive a breast cancer diagnosis as compared with women with fatty replaced breasts (1,2). Additionally, dense tissue may obscure important findings, thereby reducing the sensitivity of mammography (3,4). Women with dense breast tissue may benefit from adjunct screening imaging modalities, such as ultrasonography (US) (5). Tailoring of screening regimens on the basis of breast density and additional risk factors has been proposed (6); however, current risk prediction models do not enable discrimination sufficient to provide guidance for screening regimens (7). Breast density has been included in breast cancer risk models with the goal of improving model discrimination (8).

Current clinical practice relies on the classification of breast density into four categories as defined in the Breast Imaging Reporting Data and Reporting System (BI-RADS) (9). The classification of density using BI-RADS categories is somewhat subjective and is associated with moderate interreader variability (10,11). Thus, changes in breast density categories may be due to differences in reader selection rather than to an actual change in breast density. Variability in assigned density category may result in changes in recommendations for adjuvant

screening, such as screening US. Thus, for consistency, objectivity, and ease of use, breast density measurement ideally should be automated and accurate. Several automated software programs with which to quantitatively measure breast density are available.

The accuracy of a measurement depends on both the validity and the reproducibility of the method. Validity is assessed by comparing a measurement with a reference standard that is thought to be closest to the truth. For example, the validity of an automated measurement of breast density obtained from a mammogram may be compared with breast density obtained with a three-dimensional imaging technique, such as breast computed tomography (CT) or magnetic resonance (MR) imaging. Prior studies have found high correlation between automated volumetric breast density measurements and breast CT or MR imaging findings (12–14).

The second aspect of measurement accuracy is reliability, which is what we evaluated in our study. Reliability is defined as the extent to which a technique provides the same result if the measurement is repeated (15). A test may have excellent validity but poor reliability and vice versa. In mammography, differences in positioning, compression, and exposure parameters have been cited as possible sources of error in measurement (16).

Reliability is important in automated measurements of breast density. Automated density readings may result in recommendations for adjunct

screening and may be used in breast cancer risk assessment. A wide difference in density measurements could result in the inappropriate use of adjunct screening. In the case of breast cancer risk assessment, a large difference in breast density could potentially confer substantial changes in reported breast cancer risk.

The purpose of this study was to estimate the reliability of a reference standard two-dimensional area-based method and three automated volumetric breast density measurements using repeated measures.

Materials and Methods

Breast density software used in this study was provided by Volpara Solutions (Wellington, New Zealand) and Hologic (Bedford, Mass) under a research agreement. An author (J.A.H.) is a shareholder in Volpara Solutions and Hologic. Another author (M.J.Y.) is a shareholder in and cofounder of Volpara Solutions. All data were controlled by two authors who have no relevant conflicts of interest (G.E.M., J.T.P.).

This prospective study was approved by the University of Virginia School of Medicine institutional review board

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Abbreviations:

ABD = area breast density

BI-RADS = Breast Imaging Reporting Data and Reporting System

CI = confidence interval

Δ_{1–2} = discrepancy between the first and second breast density measurements

Author contributions:

Guarantor of integrity of entire study, J.A.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, M.J.Y., J.A.H.; clinical studies, G.E.M., M.J.Y., J.A.H.; experimental studies, O.A., G.E.M., M.J.Y.; statistical analysis, O.A., J.T.P.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

Advances in Knowledge

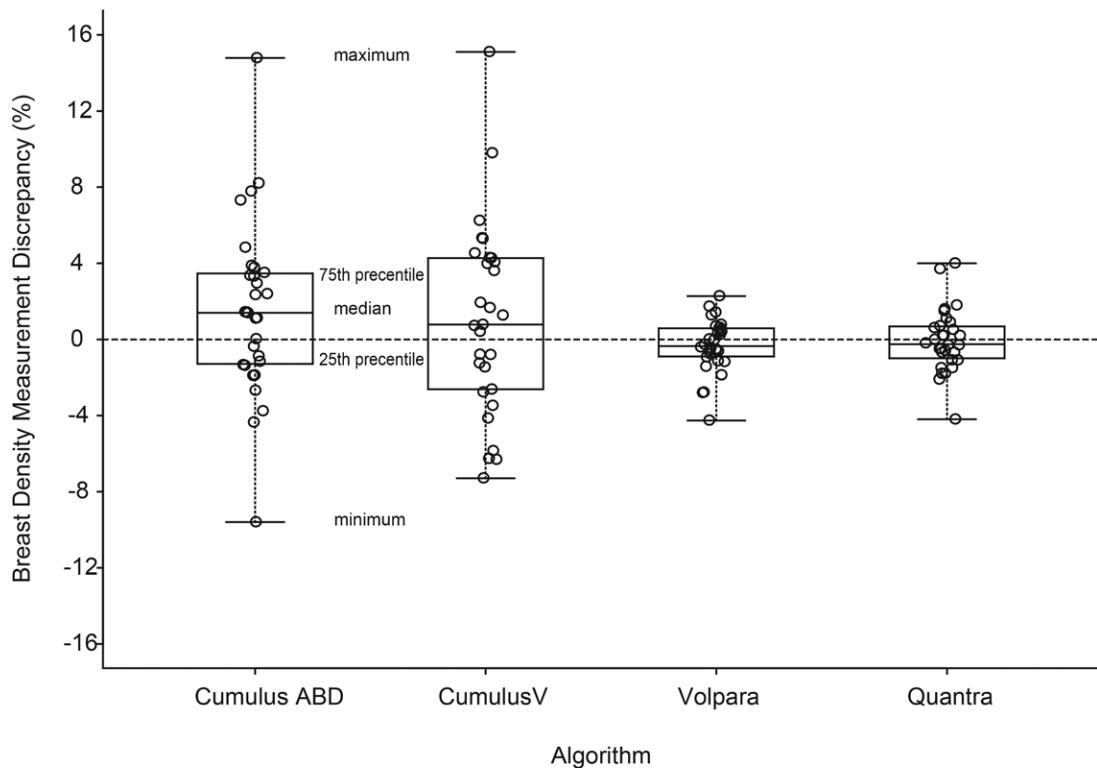
- All evaluated breast density measurement methods showed relatively low variation (intraclass correlation coefficient range, 0.96–0.98).
- Reliability was highest for Volpara and Quantra methods (within-breast density measurement standard deviation, 0.99% and 1.04%, respectively) compared with area-based Cumulus ABD and CumulusV methods (standard deviation, 3.32% and 3.59%, respectively).

Implications for Patient Care

- Automated measurement of breast density shows high reliability; thus, it may be useful in the identification of women with dense breast tissue who may potentially benefit from ancillary screening.
- Reliability is highest for Volpara and Quantra software programs, such that these programs may be better suited for incorporation in a breast cancer risk model.

Table 1**Summary Statistics for Describing the Distribution of the Replicated Breast Density Measurements**

Assessment Method and Measurement	No. of Patients	Mean (%)	Standard Deviation (%)	Standard Error (%)	Median (%)	25th Percentile (%)	75th Percentile (%)	Minimum (%)	Maximum (%)
Cumulus ABD									
1	30	23.70	18.93	3.46	17.44	8.71	33.32	2.93	77.75
2	30	22.18	17.28	3.16	16.37	9.64	33.85	2.97	69.97
Δ_{1-2}^*	30	1.52	4.52	0.82	1.40	-1.30	3.46	-9.60	14.79
CumulusV									
1	29	40.32	18.71	3.48	33.52	28.98	46.16	18.02	89.77
2	29	39.28	17.70	3.29	32.33	29.91	42.10	21.34	84.48
Δ_{1-2}^*	29	1.04	5.06	0.94	0.78	-2.62	4.28	-7.29	15.11
Volpara									
1	30	8.52	6.44	1.18	6.36	5.20	9.35	3.35	34.92
2	30	8.84	6.68	1.22	6.69	4.77	9.84	3.53	34.41
Δ_{1-2}^*	30	-0.33	1.39	0.25	-0.35	-0.90	0.58	-4.25	2.28
Quantra									
1	30	10.42	8.10	1.48	8.15	5.13	10.68	2.70	42.80
2	30	10.48	8.17	1.49	8.95	5.43	11.70	3.10	43.50
Δ_{1-2}^*	30	-0.06	1.64	0.30	-0.25	-1.00	0.68	-4.20	4.00

Figure 1**Figure 1:** Graph shows empirical distributions for Δ_{1-2} .

and was compliant with the Health Insurance Portability and Accountability Act. All study patients gave verbal

and written consent for participation. Inclusion criteria were female sex, age of at least 18 years, and presentation

for a screening mammogram. Patients were excluded if they presented with a breast problem, had breast implants,

Table 2**Breast Density Measurement Discrepancy Summary by Breast Density Algorithm**

Algorithm	Mean Within-Subject Breast Density Measurement Discrepancy (%)		Between-Subject Variability in Breast Density Measurement Discrepancy	Within-Breast Measurement Agreement		
	Estimate for Mean Δ_{1-2} (%)	P Value		Standard Deviation Δ_{1-2}	Lower Limit of Agreement Mean Δ_{1-2} Minus 2 Standard Deviations	Lower Limit of Agreement Mean Δ_{1-2} Plus 2 Standard Deviations
Cumulus ABD	1.52 (-0.17, 3.21)	.076	4.52 (3.60, 6.07)	—	-7.52 (-10.63, -5.68)	10.56 (8.72, 13.67)
CumulusV	1.04 (-0.88, 2.96)	.277	5.06 (4.01, 6.84)	—	-9.07 (-12.63, -6.98)	11.15 (9.07, 14.72)
Volpara	-0.33 (-0.85, 0.19)	.209	1.39 (1.11, 1.87)	—	-3.11 (-4.07, -2.55)	2.46 (1.89, 3.42)
Quantra	-0.06 (-0.68, 0.55)	.834	1.64 (1.31, 2.21)	—	-3.25 (-4.48, -2.68)	3.22 (2.55, 4.36)

Note.—Data in parentheses are 95% CIs.

had a history of breast cancer, or were pregnant or nursing.

Between March and May 2013, women were approached for inclusion in the study. Thirty women gave informed consent and were enrolled. All study participants underwent standard four-view screening mammography performed by one technologist as part of their usual care. After this, the primary technologist left the room and a second technologist entered and performed a second left craniocaudal examination for study purposes. The images were obtained by using a Senograph 2000D (GE Healthcare, Fairfield, Conn) or a Selenia (Hologic) machine. All mammographic images, including those from the second left cranicaudal examination, were interpreted as per usual clinical practice.

Breast Density Measurements

Breast density was measured by using both area and volumetric methods.

The area breast density (ABD) was measured on the processed images by an author (J.A.H.) with more than 20 years of experience in breast imaging and 10 years of experience in the use of the Cumulus ABD algorithm (10). Briefly, Cumulus ABD (University of Toronto) is a computer-assisted planimetry program. First, the area of the breast is determined; the user defines the skin line by using a slider bar and draws a line at the posterior aspect of the breast to exclude the pectoralis muscle. Second, each pixel within the breast area between the skin line and

the pectoral muscle is segmented into either fat or breast tissue by using a slider bar to define the threshold of the cutoff point. This is a binary process, such that each pixel is assigned to represent either fat or breast tissue. There is no accounting for how white or gray a pixel may appear (pixel depth). This method has high reproducibility between users and is considered the reference standard, as it is the most validated regarding an association with breast cancer risk (1,2,17).

Three automated volumetric measures were evaluated: CumulusV (University of Toronto), Volpara (version 1.4.5; Volpara Solutions), and Quantra (version 2.0; Hologic, Danbury, Conn). Automated breast density measurements were obtained by using the raw digital mammogram. Like the Cumulus ABD method, the volumetric density software first defines the area of the breast by defining the skin line and excluding the pectoral muscle. Unlike the area-based method, volumetric software attempts to estimate the three-dimensional volume of breast tissue by taking pixel depth into account. For example, a pixel that is 50% gray would be considered to be breast tissue with Cumulus ABD; however, it would be considered to contain half breast tissue and half fat with volumetric software. Thus, the volumetric methods are expected to result in lower percentage breast density values. There are also some intrinsic differences between the volumetric methods used to measure breast density.

The CumulusV algorithm was developed at the University of Toronto (14,18). Briefly, it deduces the composition of the breast from the breast thickness and the x-ray attenuation obtained from the digital image of a given mammography system, where the x-ray attenuation of breast tissue as a function of thickness and composition previously has been calibrated. In addition, an algorithm is used to correct for the readout thickness of the mammography machine, which can often be erroneous (14,19–21). Both mammography machines used in our study underwent calibration as follows: a set of breast phantoms were imaged with clinically relevant x-ray techniques to obtain the calibration of image signal versus breast thickness and composition. Next, an elastic breast phantom was compressed at different forces, and its true thickness was measured. The difference between the true thickness and the readout thickness of the machine as a function of compression force was used to deduce the correct breast thickness from the mammograms. CumulusV includes the skin in the estimation of fibroglandular volume, while Volpara and Quantra do not.

The Volpara method uses image processing techniques to determine a reference pixel of all fat; it then compares all other pixels to that reference pixel to determine the difference in x-ray attenuation and thus tissue composition. Use of a reference pixel reduces dependence on accurate breast thickness and completely removes the need

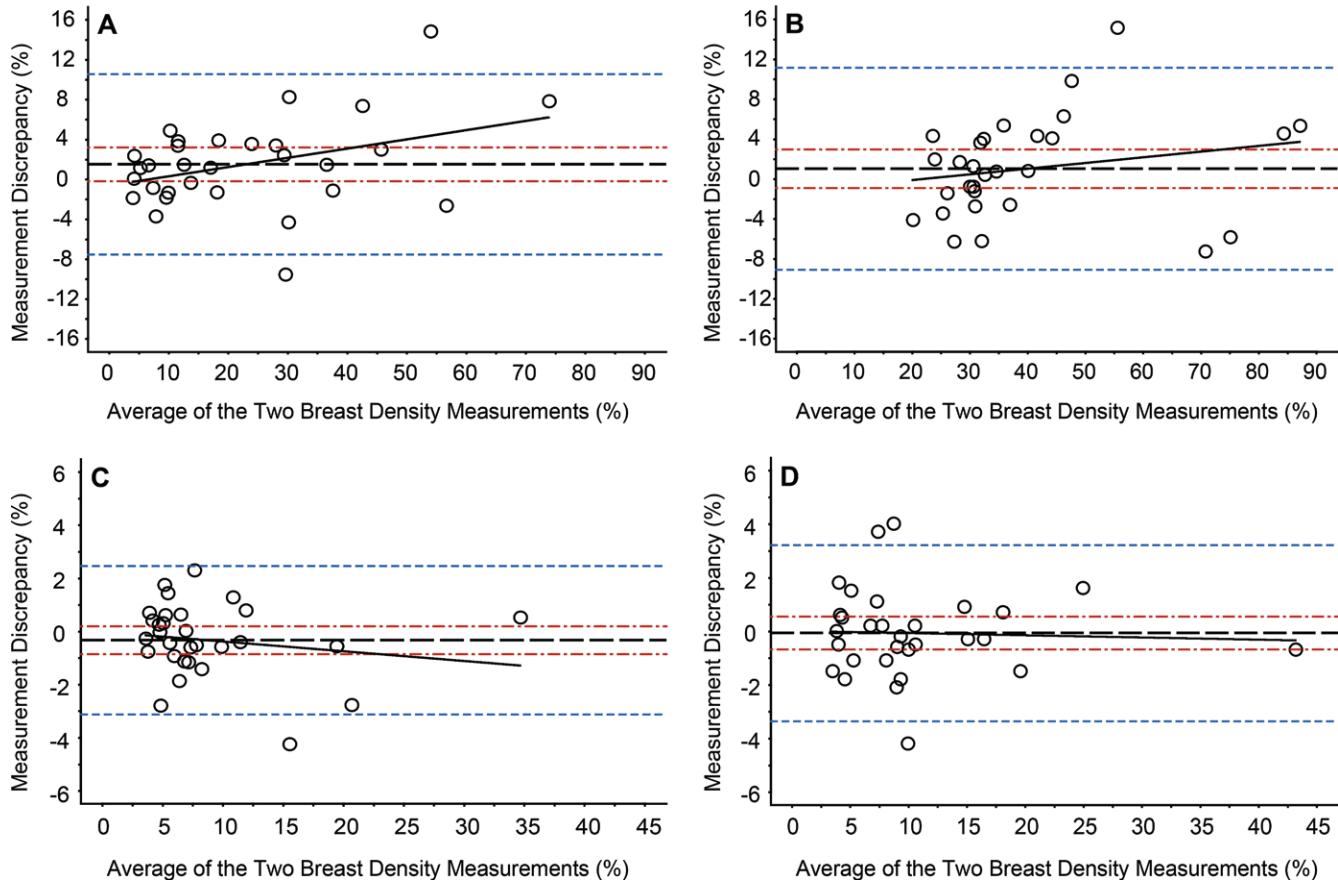
Figure 2

Figure 2: Graphs show relationship between Δ_{1-2} and the average of the two breast density measurements for, *A*, Cumulus ABD, *B*, CumulusV, *C*, Volpara, and, *D*, Quantra algorithms. Solid black lines indicate the regression of best fit, dashed black lines indicate the mean measurement discrepancy, red dashed lines indicate the lower and upper boundaries for the 95% CI for the mean measurement discrepancy, and dashed blue lines indicate the lower and upper limits of measurement agreement (ie, mean $\Delta_{1-2} \pm 2$ standard deviations). Note that under the assumption that the values for Δ_{1-2} are normally distributed, 95% of the Δ_{1-2} values would be expected to be within 2 standard deviations of the mean Δ_{1-2} .

to know certain physics parameters, such as tube current and detector type (22).

Quantra software is used to estimate the two-dimensional thickness distribution of fibroglandular tissue in the image on the basis of the two-compartment (fat and dense tissue) x-ray absorption model. Quantra software uses “For Processing” images to perform breast tissue segmentation and estimate the thickness of fibroglandular tissue at each pixel inside the breast region by using a proprietary algorithm. The algorithm also estimates the breast thickness for calculation of total breast volume. The breast density is calculated

by dividing the estimates of total fibroglandular tissue volume divided by breast volume.

Statistical Analysis

Overview.—As stated in Röhrig et al, “measurement reproducibility (ie, measurement agreement) is the extent to which a measurement technique consistently provides the same results if the measurements are repeated” (15). Excellent reproducibility is therefore reflected by: (a) the discrepancy between replicate measurements being small, (b) the discrepancy between replicate measurements being independent of the magnitude of the

measurements, and (c) the discrepancy between replicate measurements having small variability.

Analysis of measurement discrepancy.—For each breast density algorithm, we subtracted the second breast density replicate measurement from the first to produce a set of Δ values (Δ_{1-2}) that represented the within-breast density measurement discrepancy. The Δ_{1-2} values of each breast density algorithm were then analyzed with a random-effects model. The random-effects model parameter estimates for mean Δ_{1-2} and the standard deviation of Δ_{1-2} were used to determine the Bland-Altman within-breast

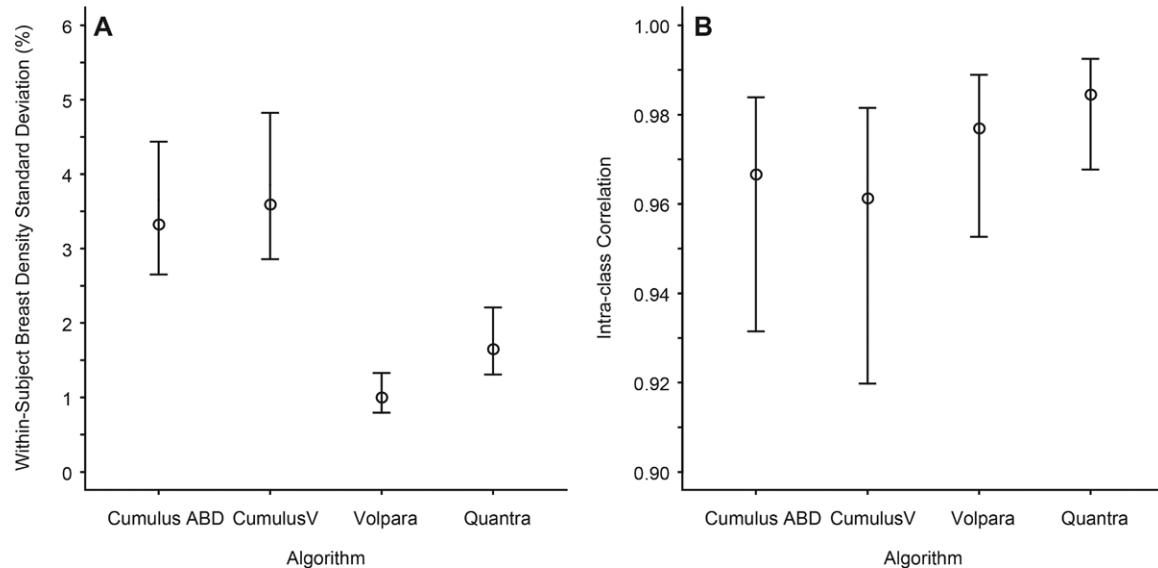
Figure 3

Figure 3: Graphs show breast density measurement precision on, *A*, repeat assessments and, *B*, intraclass correlation. Vertical lines identify the extent of the 95% CI. ○ = the point estimate.

density lower and upper measurement agreement limits (ie, mean $\Delta_{1-2} \pm 2$ standard deviations), and associated 95% confidence intervals (CIs) (23). Note that if the values for Δ_{1-2} follow a normal probability distribution, 95% of the Δ_{1-2} values would be expected to be within 2 standard deviations of the mean of Δ_{1-2} measurement distribution.

To compare the mean Δ_{1-2} values of the four different breast density algorithms, we used the linear contrasts of the least square means Δ_{1-2} values of a linear mixed-effect model as the pivotal quantities of the hypothesis test procedure. The null hypothesis rejection criterion was based on a Tukey multiple comparison two-side type I error rate that restricted the entire set of hypothesis tests to have a combined two-sided type I error rate of 0.05. The same statistical method was used to compare the distributions of the averages of the two replicate breast density measurements between the four different breast density algorithms.

To determine if there was a systematic relationship between Δ_{1-2} and the average of the two breast density measurements, Spearman correlation

analyses were conducted. A $P \leq .05$ decision rule was used as the null hypothesis criterion.

Analysis of breast density measurement precision.—For each algorithm, a random-effects model was used to estimate the within-subject variability of the two breast density measurements from the same breast. Additionally, for each algorithm, an intraclass correlation coefficient was estimated based on the between-subject and within-subject variance components of the random-effects model. The 95% CI construction for the intra-class correlation coefficient was based on the confidence interval method of Fleiss and Shrout (24). Note that the intraclass correlation coefficient is a statistic that quantitatively summarizes how strongly units in the same group resemble each other (ie, for the present case, how strongly the two density measurements from the same breast resemble each other). Intraclass correlation values close to 1 indicate a high degree of measurement homogeneity.

Mammographic images and parameters for the largest difference between measures were evaluated for each algorithm.

All of the aforementioned statistical analyses were conducted by using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

Thirty women were recruited to the study. Mean patient age was 60 years (age range, 42–90 years). BI-RADS breast density categories as reported in the screening study were fatty in seven women (23%), scattered in 14 women (47%), heterogeneous in eight women (27%), and extremely dense in one woman (3%). Mean body mass index was 26.7 kg/m² (range, 19.3–40.7 kg/m²); 16 women (53%) were of normal weight, seven (23%) were overweight, and seven (23%) were obese.

All 30 cases were analyzed by using Cumulus ABD, Volpara, and Quantra. One case could not be analyzed with CumulusV because the compression thickness readout was zero; this algorithm requires compression thickness to calculate volumetric density. For this algorithm, this case was excluded.

The distributions of the average of the two breast density measurements were considerably higher with Cumulus

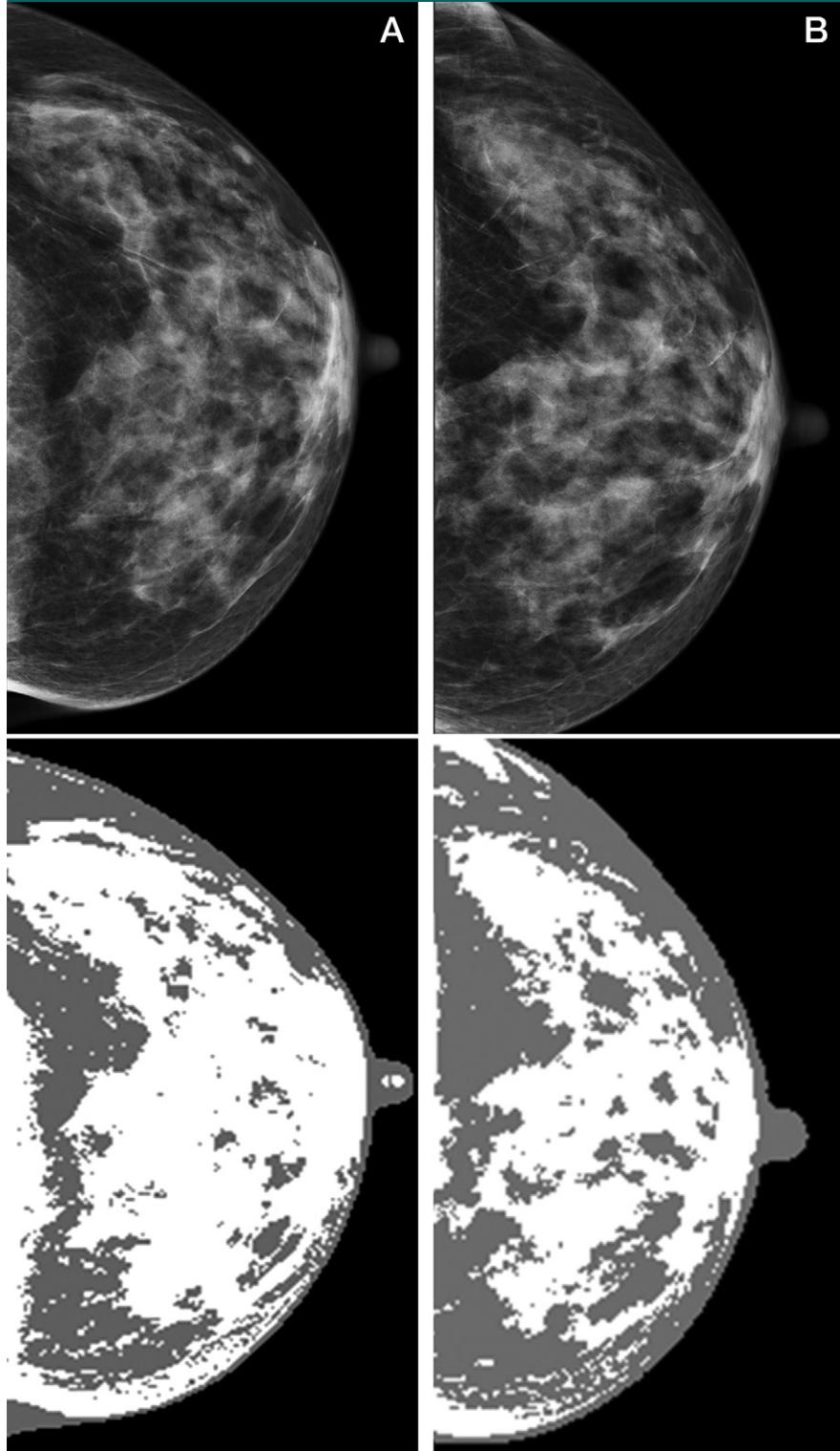
Figure 4

Figure 4: Mammograms (top) and segmentation images (bottom) show the largest outlier between the left craniocaudal measurements using the Cumulus ABD algorithm. The density measures of the, *A*, first and, *B*, second images were 61.4% and 46.6%, respectively. The positioning is different between the two views, but the thresholding for segmentation is also somewhat lower for *B*.

ABD and CumulusV than with Volpara ($P < .001$ and $P < .001$, respectively) and Quantra ($P = .001$ and $P < .001$, respectively) (Table 1).

The empirical distributions for the within-breast Δ_{1-2} in Figure 1 show considerably higher variation for Cumulus ABD and CumulusV than for Volpara and Quantra. The estimates for mean Δ_{1-2} are provided in Table 2 along with the estimates for between-subject variability in the Δ_{1-2} measurement and the limits for within-breast measurement agreement (ie, mean $\Delta_{1-2} \pm 2$ standard deviations). With regard to mean Δ_{1-2} , there were no algorithm-versus-algorithm differences in mean Δ_{1-2} ($P > .150$ for all algorithm-versus-algorithm comparisons).

For each breast density algorithm, the relationship between Δ_{1-2} and the average of the two breast density measurements is depicted in Figure 2. For the Cumulus ABD algorithm, there was a marginal positive correlation between Δ_{1-2} and the average of the two breast density measurements ($r_s = 0.32$; 95% CI: -0.06 , 0.61 ; $P = .087$). For CumulusV, there was a positive correlation between Δ_{1-2} and the average of the two breast density measurements ($r_s = 0.36$; 95% CI: 0.00 , 0.66 ; $P = .042$). For Volpara, there was no correlation between Δ_{1-2} and the average of the two breast density measurements ($r_s = -0.17$; 95% CI: -0.51 , 0.20 ; $P = .352$). Similarly, for Quantra, there was no correlation between Δ_{1-2} and the average of the two breast density measurements ($r_s = -0.09$; 95% CI: -0.45 , 0.29 ; $P = .633$).

Breast Density Measurement Precision

Precision was better for Volpara and Quantra than for Cumulus ABD or CumulusV. The within-breast density

measurement standard deviation was 3.32% (95% CI: 2.65, 4.44) for Cumulus ABD and 3.59% (95% CI: 2.86, 4.48) for CumulusV (Fig 3). The within-breast density measurement standard deviation was 0.99% (95% CI: 0.79, 1.33) for Volpara and 1.64% (95% CI: 1.31, 2.21) for Quantra.

The intraclass correlation was 0.97 (95% CI: 0.93, 0.98) for Cumulus ABD and 0.96 (95% CI: 0.92, 0.98) for CumulusV (Fig 3b). The intraclass correlation was 0.98 (95% CI: 0.95, 0.99) for Volpara and 0.98 (95% CI: 0.97, 0.99) for Quantra.

Evaluation of mammograms with the greatest difference between measurements revealed some potential explanations for the variance (Figs 4–7). Differences in readings were largely thought to be due to differences in compression or positioning.

Discussion

Concern has been raised regarding reliability of automated measurement of breast density, as differences in positioning, compression, and technical parameters may potentially have marked effects on measurements (25). The results of our study show that volumetric measures obtained using the Volpara or Quantra algorithms have excellent reliability for repeated measures, while the Cumulus ABD and CumulusV measures have moderate reliability.

Variability in density readings in our study was likely due to differences in positioning, as shown in the figures. Differences in positioning may result in differing amounts of breast tissue being included in the image for evaluation. For most of the patients in our study, differences between the original and repeated image were minimal. However, this may not be the case if the standard of care for adequate depth is not met during positioning of the patient for imaging. An example in the literature shows how the density measurement can vary widely (27% and 13%) due to differences in positioning of two craniocaudal views (25). However, in the example provided, the

Figure 5

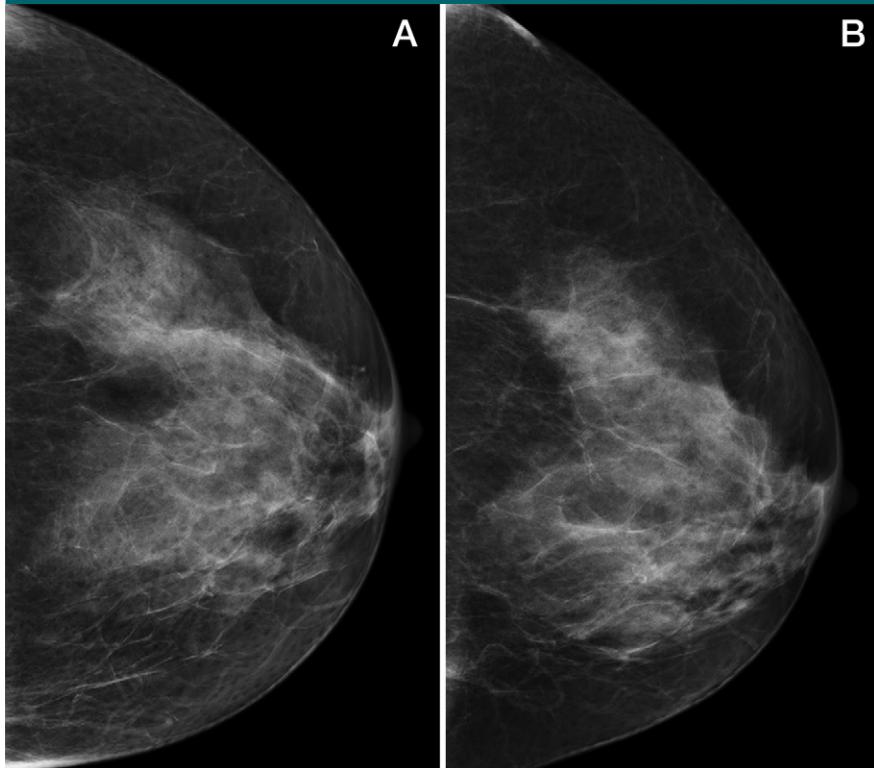


Figure 5: Mammograms show the largest outlier between the left craniocaudal measurements with the CumulusV algorithm. The density measures of the, *A*, first and, *B*, second images were 63.0% and 47.9%, respectively. In *A*, the image was obtained with greater compression (70 N), resulting in a smaller breast thickness (39 mm) when compared with *B* (50 N, 46-mm thickness). The corrected thickness was likely erroneous.

first image that is higher in density did not meet the standard of care for positioning, as it excluded much of the posterior breast; this is likely why imaging was repeated by the technologist (25). Images used for density measurement should be at the level of standard of care for depth of tissue included and be free of blur or other artifacts.

Occasionally, technologists will obtain additional images beyond the four typical views obtained for screening (bilateral craniocaudal and mediolateral oblique). These may be obtained due to incomplete coverage of the breasts because of small receptor size, often referred to as tiled images. Likewise, a technologist may obtain a nipple-in-profile view to complete a study that is labeled as a craniocaudal view but includes only a small area of

the breast. The density measurement of these views that are beyond the routine images may result in an outlier value when compared with those obtained from the routine craniocaudal and mediolateral oblique views. Some automated density software programs (Volpara and Quantra) provide a mean breast density by averaging the density measured on all views, and this may minimize the effect of outlier values for an individual patient. The management of outlier values is a similar but different topic than that addressed in this study.

Mammography machines are designed to obtain an image that is clinically optimized to detect breast cancer. They are not designed to have high accuracy in the measurement of compressed breast thickness. This lack of

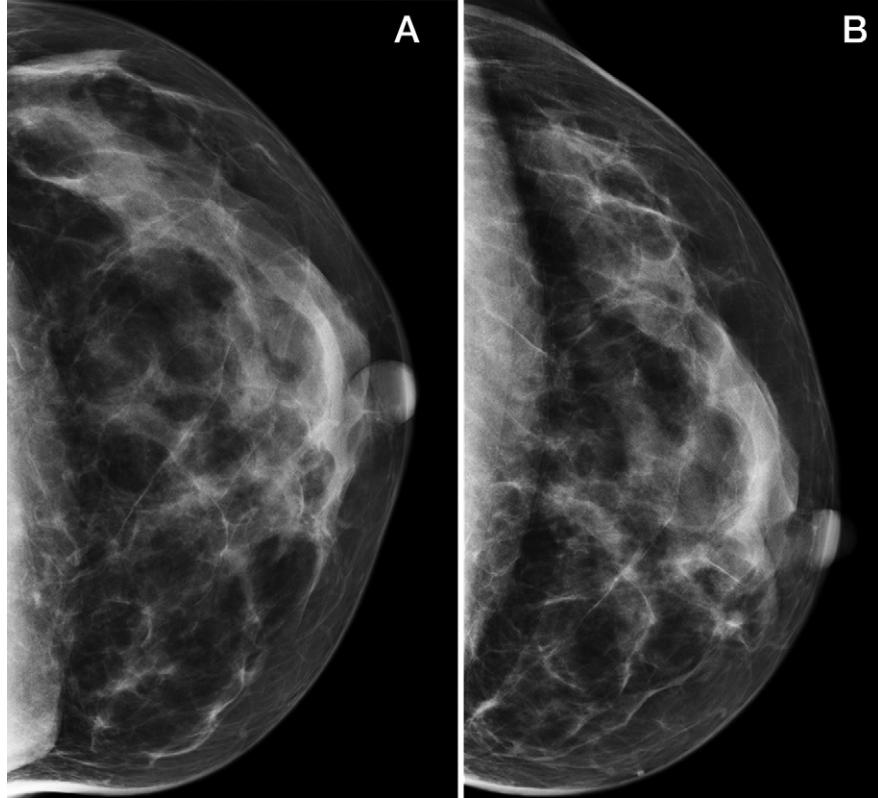
Figure 6

Figure 6: Mammograms show the largest outlier between the left craniocaudal measurements with the Volpara algorithm. The density measures of the, *A*, first and, *B*, second images were 17.6% and 13.4%, respectively. The dense tissue is more spread out on *B*; the differences are likely due to positioning.

accuracy of compressed breast thickness readout can be compensated for by using calibration (CumulusV), including a reference phantom in the image (26), or internal calibration of a fat pixel (Volpara). The higher variability in density measurements for CumulusV compared with Volpara seen in our study was likely due to differences in management of the compressed breast thickness readout.

Variability in technical exposures is not likely to substantially affect density measurement using automated software unless the image is markedly under- or overexposed. Substantial variation does exist in image processing. However, the automated breast density software programs all use the raw ("For Processing") images rather than the processed ("For Presentation") images. Because Cumulus ABD measurements

rely on visual assessment to segment the image into fat and breast tissue, processed images are typically used for this technique.

Our study did not address the validity of the measurement of breast density, which is best evaluated by comparison with a three-dimensional imaging method, such as MR imaging or CT.

A recent study comparing automated breast mammographic density measures obtained using Volpara with breast MR imaging in 186 women at high risk found high correlation (12); Pearson correlation coefficients were 0.93, 0.97, and 0.85 for volumetric breast density, breast volume, and fibroglandular volume, respectively. A preceding similar but smaller study of 99 women at high risk was performed to evaluate correlation with breast MR imaging using both Quantra and

Volpara (13); correlation coefficients were 0.51, 0.91, and 0.40, respectively, for volumetric breast density, breast volume, and fibroglandular volume using Quantra and 0.73, 0.91, and 0.63, respectively, using Volpara. Although we did not evaluate this important aspect of the validity of the density measurement in our study, the results from these two studies suggest that the correlation is very good between automated volumetric measures and cross-sectional imaging.

In the United States, there are currently more than a dozen states with laws that require communication of high breast density (typically including women with heterogeneous or extremely dense breasts using the BI-RADS categories) to patients undergoing mammography; many require an additional statement that women with dense breast tissue may benefit from additional screening with modalities such as US or MR imaging. Interreader agreement for use of BI-RADS categories is only moderate (10,11,27); thus, identification of women with dense breasts may vary between readers. The translation of automated breast density measurements into four categories that approximate the BI-RADS categories has been proposed (12) and may eventually be a more consistent method of identifying women who may potentially benefit from additional screening. More research is needed before this will be known.

Since breast density is a moderate risk factor for breast cancer, its inclusion in a breast cancer risk model should improve model discrimination. Tice et al included BI-RADS density categories in a breast cancer risk model, but this did not improve model discrimination (28). However, dividing a risk factor into categories reduces model sensitivity when compared with use of a continuous variable. Thus, inclusion of a density measurement that is a continuous reproducible measure may improve model discrimination even when inclusion of BI-RADS density categories does not. A possible detriment to including a density measurement in a risk model is that if

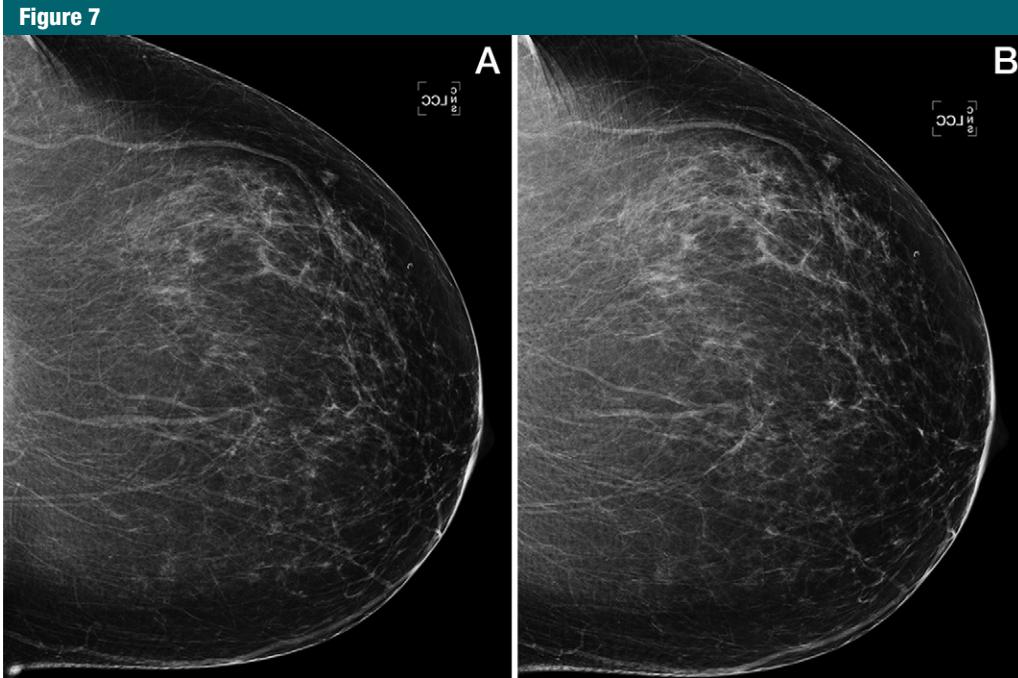


Figure 7: Mammograms show the largest outlier between left craniocaudal measurements with the Quantra algorithm. The density measures of the, *A*, first and, *B*, second images were 5.3% and 11.3%, respectively.

there is significant variability when repeated in the same patient, the inclusion of this risk factor could misrepresent the outcome of breast cancer risk produced by the model. Fortunately, our study showed that the variability of breast density measurement using Volpara or Quantra is low and that the high reliability of these methods should allow their inclusion in breast cancer risk prediction models.

Our study had some limitations. The sample size was small, and different results would be possible if the sample size was larger. Since 70% of our study population was classified as having fatty or scattered density with BI-RADS categories, our results may have been different if more women with heterogeneous or extremely dense tissue had been included. The repeated images were all obtained with the same machine, and different values may have been obtained if we had used different machines. In addition, our study was focused only on the reproducibility of the measurement of breast density and did not address validity.

In summary, our study showed excellent reproducibility of breast density measurement with the Volpara and Quantra algorithms and moderate reproducibility with the Cumulus ABD and CumulusV algorithms. The excellent reproducibility of automated breast density measurements indicates that they would be well suited for inclusion in a breast cancer risk model.

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Does Mammographic Density have an Impact on the Margin Re-excision Rate After Breast-Conserving Surgery?

- Brandy L. Edwards, Christopher A. Guidry, Krista N. Larson, Wendy M. Novicoff, Jennifer A. Harvey, Anneke T. Schroe

Background

Limited and conflicting data exist on an association between mammographic density (MD) and re-excision rates after breast-conserving surgery (BCS). Additionally, the correlation of MD with resection of unnecessary margins during initial BCS is unknown.

Methods

All women with a diagnosis of breast cancer from 2003 to 2012 and enrolled in a larger study on MD were evaluated. Operative and pathology reports were reviewed to determine margin resection and involvement. Mammographic density was determined both by breast imaging-reporting and data system (BI-RADS) classification and by an automated software program (Volpara Solutions). Additional margins were deemed unnecessary if the lumpectomy specimen margin was free of invasive tumor [≥ 2 mm for ductal carcinoma in situ (DCIS)] or if further re-excision was needed.

Results

Of 655 patients, 398 (60.8 %) had BCS, whereas 226 (34.5 %) underwent initial mastectomy. The women with denser breasts (BI-RADS 3 or 4) underwent initial mastectomy more frequently than the women with less dense breasts (40.0 vs. 30.5 %, respectively; $p = 0.0118$). Of the patients with BCS, 166 (41.7 %) required separate re-excision. Additional margins were taken during BCS in 192 (48.2 %) patients, with 151 (78.6 %) proving to be unnecessary. In the bivariable analysis, the patients with denser breasts according to BI-RADS classification and volumetric density showed a trend toward requiring more frequent re-excision, but this association was not seen in the multivariable analysis. The rate of unnecessary margins did not differ by breast density. In the multivariate analysis, the re-excision rates increased with DCIS ($p < 0.0003$) and decreased with resection of additional margins ($p = 0.0043$).

Conclusions

Mammographic density is not associated with an increased need for re-excision or resection of unnecessary margins at initial BCS.

What Do Women Know About Breast Density? Results from a Population Survey of Virginia Women¹

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Abstract (247/250 possible words**)**

Background: Breast density reduces the sensitivity of mammography and is a moderate independent risk factor for breast cancer. Virginia is one of 21 states that currently require providers to notify patients when they have dense breasts (1.). However, little is known about what women in the general population know and understand about breast density. This survey study assessed knowledge about breast density and about its impact on mammography and its relationship to breast cancer risk.

Methods: A random sample of 1024 Virginia women between age 35-70 years without breast cancer, reached by landline and cell phone, completed a 24-minute interview in English or Spanish.

Results:

Thirty-six percent of respondents had been informed about their breast density by a doctor. These women were more likely to be familiar with the term “breast density.” Seventy-five percent of respondents reported being either somewhat or very familiar with risk factors for breast cancer, but less than 1% spontaneously listed breast density as a risk factor. Few respondents (5.3%) were able to answer three breast density knowledge questions correctly. Low-education, African-American and Jewish women were less knowledgeable about breast density.

Conclusion:

These results suggest that while women are becoming aware of the term “breast density”, they may not understand its relationship to cancer detection on mammography and, especially, its relation to breast cancer risk.

Impact:

Improved education about breast density—for both the public and for providers—is necessary to augment new legislation to help women evaluate and manage their breast cancer risk.

Introduction

Breast density is a moderate independent risk factor for breast cancer (2) and reduces the sensitivity of mammography (3), yet women may not know or understand the implications of their personal breast density on cancer risk or detection. Women in at

¹ This study was supported by CDMRP BC100474.

least 21 states are subject to ‘density notification laws’ that require radiologists to inform women of their breast density, and federal bills have been proposed in the last three congressional sessions. The assumption underlying these laws is that women will use this information to make decisions about breast cancer screening with their healthcare providers.

Breast density is currently classified using subjective visual assessment by the radiologist into one of four categories: almost entirely fatty; scattered fibroglandular densities; heterogeneously dense; or extremely dense (4). The American College of Radiology’s most recent published data on breast cancer screening practices in the United States finds approximately 50% of all women screened annually will fall into one of the two reportable high-density categories (5, 6). In the United States, this means that approximately 19 million women will be notified they have dense breasts this year (7) and many, if not most, will be unclear about its meaning for their personal breast health (8, 9). Relatively little has been documented regarding women’s knowledge about breast density, how it affects the sensitivity of mammograms, the degree to which it is a risk factor for cancer and how it affects their actual and perceived risk of breast cancer. (10). Women have been thrust into the current and ongoing debate over screening mammograms: their frequency; relevance; diagnostic accuracy and implications for treatment (11, 5, 10). Now these women have another factor to consider when making personal decisions about their breast health: breast density.

The current body of research on women’s knowledge of breast density is limited. Smaller studies have found that when women were provided with information on breast density, they were able to identify density as a risk factor for breast cancer, but knowing that information did not contribute to increased anxiety, nor did the information alter their screening behaviors (8). Other studies have suggested that race does not appear to be a significant factor in knowledge: both black and white women were found to be equally unaware of breast density as a risk factor for breast cancer. Education does appear to be a significant factor in knowledge and awareness: in one study, college educated women were better able to accurately identify density, and this was corroborated in another smaller study of women that found that having heard the term ‘breast density’ correlated with being older than 50, white, educated and higher-income. Additionally, women residing in Connecticut, where the mandatory density reporting legislation was initiated, were much more aware of the term ‘breast density’ and its impact on breast cancer risk (10; 12). Most of these studies are based on small or clinically-based samples; others have used non-probability samples (13). The one large-scale study (12) surveyed participants in a pre-recruited, online access panel and did not directly survey the general population.

The Virginia “Breast Density” notification law went into effect on July 1, 2012; the law requires the radiologist/office performing the screening mammogram to include a specific statement in their mammogram result letter if they have dense breast tissue (14). Our study sought to explore what women in Virginia know about breast density and its risks for cancer detection, diagnosis, and recommendations. Women need to understand breast density and its implications for personal cancer risk and reduced detection to enable more informed decision-making surrounding their breast health.

This study is, to our knowledge, the first large-scale survey to address these questions by directly recruiting women from the general population.

Methods

The Virginia Survey on Breast Cancer Screening was conducted via telephone by the UVa Center for Survey Research (CSR) during the summer and early fall of 2013.

Questionnaire development

Prior to drafting the questionnaire, CSR conducted two focus groups, one with breast cancer survivors and one with women who have never had breast cancer. Two breast cancer advocates, who are active members of the study team, helped to conduct focus groups.

The survey questionnaire included questions about breast cancer screening adapted from the Mayo Clinic Long Term Follow-up Study (15) as well as a number of new questions developed expressly for this study. After several rounds of review and edits by the study team, CSR conducted a second round of focus groups in early 2013, designed as group self-administered pre-tests followed by a group debriefing. The first group was conducted in Charlottesville, Virginia, and the second was conducted in Richmond, Virginia, an area with a more ethnically diverse population. Women ages 35 to 70 years who had not had breast cancer were recruited by telephone from random samples of listed households in Charlottesville and Richmond, Virginia, and a list of cell phone numbers in Richmond. The feedback from these two sessions was used to fine-tune the presentation of breast density and the ways in which respondents were asked about their own perception of their breast cancer risk.

After revision, the programmed questionnaire was critiqued by a team of experienced telephone interviewers at CSR. Finally, a live telephone pre-test of the instrument was conducted in May of 2013, yielding 26 completed interviews. The final questionnaire, in English and Spanish, covered a number of topics in sequence: the respondent's family experience with breast cancer, her current breast cancer screening practices, her assessment of her own risk for breast cancer, understanding of breast density, understanding of current screening guidelines, willingness to change screening practices, sources of information about breast cancer screening, and demographics.

Sample

The survey used a triple-frame telephone sample of Virginia phone numbers (16), combining a conventional random-digit landline telephone sample, a sample of directory-listed landline telephone number, and a random-digit cell phone sample with active numbers identified. The survey instrument included an initial screener that asked for women aged 35 to 70 and screened out women with a prior diagnosis of breast cancer and those not residing in Virginia. For households reached via landline, respondents were asked to say how many women in the household met the eligibility criteria, and then a random selection procedure (17) was used to select one of these women as the respondent. For cell phone interviews, the person answering was simply screened for eligibility.

Interviewing

All interviewing was conducted by trained, female interviewers from June through October, 2013. The average interview length was 24 minutes and 1,024 interviews (pretest included) were fully completed with an additional 27 usable partial interviews. The response rates, calculated using AAPOR standard rate RR4 (18), varied by sampling frame yielding an overall response rate to the survey of 24.5 percent.

Weighting and margin of error

The survey data were weighted to match the distributions of age, race, ethnicity, marital status, homeownership and education among Virginia women ages 35-70, based on the 2011 American Community Survey (19). Using a raking method, final survey results were weighted for demographic characteristics, region of the state, and telephone service type. Since the prevalence of cell-phone-only status among Virginia women ages 35 to 70 is not known, a bootstrap method was used to estimate the population percentages in each phone segment, as described by Guterbock (20). The weighted sample is thus closely reflective of the demographic characteristics of all Virginia women ages 35-70, their regional distribution and their telephone status. The overall design effect from weighting was 1.8, yielding a margin of error of ± 4.1 percent at the 95% level of confidence. All analyses reported here use the complex sampling facility of SPSS 21 to obtain OLS regressions that take into account the design effect from weighting.

Results

Table 1 summarizes demographic and personal history information for the weighted sample of survey respondents. About 12% of the weighted sample had been diagnosed with cancer of any kind, and roughly 40% of respondents have one or more blood relatives who have been diagnosed with breast cancer.

[TABLE 1 ABOUT HERE]

Screening and Risk

More than 90% of women in this study said they have done something in the last five years to check themselves for breast cancer. Three-fourths of these women have had a mammogram in the last five years. More than 50% do breast self-examinations, and 40% have had some type of clinical breast exam. For those who have had a mammogram, more than 40% have received abnormal results.

In order to understand what women think about their own risk for breast cancer, respondents were asked to estimate their chance of getting breast cancer in the future. About half of the women said their risk of getting breast cancer is the same as any other woman. Thirteen percent said they feel their risk of getting breast cancer is more than the average woman, while nearly one-third said their risk is less. When asked how

familiar they are with the risk factors for breast cancer, 9 out of 10 said they were at least slightly familiar. One-third of the women said they were very familiar with the risk factors.

Women were asked to list any factors they knew that affected a woman's risk of developing breast cancer, either increasing or decreasing the risk. **Error! Reference source not found.** shows the various factors that women listed in response to this open-ended, unprompted question. Breast density was mentioned as a risk factor by only 0.8% of the respondents, ranking twenty-second by frequency of mention.

[FIGURE 1 ABOUT HERE]

Breast Density Familiarity and Being Informed of Density

When asked how familiar they are with breast density, fewer than 1 out of 5 women said they were very familiar with the concept. Four out of 10 reported being somewhat or slightly familiar, and one third said they were not familiar with the concept.

About 39 percent of the women surveyed said their health care provider had informed them about the density of their breasts. Women who have had mammograms were more likely to have been informed (Table 2). In fact, over half of women who have had a mammogram in the last year report that they have been informed about the density of their breasts. Nevertheless, one-third of the women who have had mammograms said they were not familiar with the concept of breast density at all. And among women who have been informed about the density of their breasts, 53% said they had never heard anything about the relationship of breast density to the risk of breast cancer.

[TABLE 2 ABOUT HERE]

Breast Density Knowledge

Three questions were used to measure respondents' knowledge of breast density. Only 25 percent of the women in the study said they had heard anything about the relationship between breast density and breast cancer risk. Respondents who said they had heard something about the relationship of breast density to breast cancer risk were asked whether the risk of breast cancer is higher for a woman with high breast density and whether it will be harder to detect a tumor for a woman with high breast density. Of those who had heard of the relationship, 85 percent knew that it would be harder to detect tumors in a woman with dense breasts; this represents 20 percent of all women in the sample. Fifty-four percent knew that a woman with dense breasts would have a higher risk of breast cancer; this is just 13 percent of the entire sample. The results thus indicate that the relationship between breast density and lower sensitivity of mammography is more familiar to women than the link between density and cancer risk, but the great majority of women are unfamiliar with (or unclear on) either relationship.

Those who said they had some familiarity with breast density were asked which methods can be used to identify breast density. Nine out of ten of these women

correctly said that breast imaging, such as a mammogram, CT scan, or MRI, can be used to identify breast density. However, 20 percent also said the size and shape of the breasts can be used; one-third said a breast self-examination can be used; and nearly half said that a breast exam by a medical professional can be used to identify breast density.

To summarize the accuracy of women's knowledge, each respondent was assigned a point score ranging from 0 to 4. One point was assigned for choosing a correct answer on each of the three knowledge questions, and an additional point was assigned to those who chose the correct answer on the question about breast density detection and did not also choose any of the incorrect alternatives. Only about 5% of women with some knowledge of breast density had all three questions fully correct (Figure 2).

[FIGURE 2 ABOUT HERE]

Correlates and Predictors of Breast Density Knowledge

Familiarity with the concept of breast density and knowledge of its relationship to breast cancer detection and breast cancer risk are correlated with a variety of personal and social factors, as seen in the bivariate correlations shown in Table 3. The table shows results (bivariate linear correlations with the design effect from weighting taken into account) for three indicators of such knowledge: a woman's self-rated familiarity with the term "breast density," her report of whether or not she had heard anything about the relationship of breast density to breast cancer risk, and her score on the four-point scale of accuracy of breast cancer knowledge, described above. The strongest single correlate for each of the three indicators is whether or not the woman's health care provider had informed her about the density of her breasts. Each of the indicators is strongly correlated with indicators of more general knowledge and awareness about breast cancer: familiarity with the risk factors for breast cancer, and familiarity with current recommendations for breast cancer screening. Women who see themselves as being at higher than average risk for breast cancer are significantly higher on all three indicators. The strongest social and demographic correlates are indicators of socio-economic status: breast cancer familiarity and knowledge are higher for more educated women, those with higher household incomes, and those who own their own homes. Older women are significantly more familiar with breast density and more accurate in their knowledge of its effects. In addition, African-American women score lower on all three indicators, current smokers score lower on two of the indicators, and Ashkenazi Jewish women are less likely to have heard about the density-cancer link. These correlations are all useful as descriptors of which women are currently more or less knowledgeable on this subject.

To better understand the underlying factors creating disparities in familiarity and knowledge, a multivariate analysis was conducted; Table 4 displays the results. As the bivariate correlations suggested, one strong predictor for all three indicators is whether a woman has been informed of her breast density by her health care provider. Level of education is a predictor for all three indicators, but (with these and other factors and covariates controlled) the other indicators of socio-economic status (including current

smoking) are generally no longer significant as predictors (although home ownership is still significantly predictive of accuracy of breast cancer knowledge). Age is no longer significant with other variables controlled. For two of the three indicators, African-Americans remain somewhat less familiar and knowledgeable than others, even with socio-economic indicators controlled; however, the coefficients for African-American status are smaller in the multivariate result than in the bivariate result, suggesting that some—but not all—of the bivariate race effect is associated with education and socio-economic differences between blacks and other Virginia women.

An unexpected finding that emerges in the multivariate results is that women of Ashkenazi Jewish descent are significantly lower on all three indicators of familiarity and knowledge, with other factors controlled. As expected based on the general socio-economic status of Jewish Americans (21), the Ashkenazi women (less than three percent of our sample) are substantially above the statewide mean in education and household income; they are concentrated in urban regions of the state and none resides in a medically underserved area. The coefficients for Ashkenazi background are stronger in the multivariate regression than they are in the bivariate correlations. These results indicate that Ashkenazi women in Virginia are overall only a little below average in their familiarity and knowledge of breast density, but that they are far below the knowledge levels one would predict given their high socio-economic status.

[TABLE 3 ABOUT HERE]

[TABLE 4 ABOUT HERE]

Discussion

The current body of research on women's knowledge of breast density is limited. Most prior studies of women's knowledge were based on small samples or used clinically based samples that do not fully represent the broader population of women. The results reported here come from a probability-based, general population sample of more than 1,000 women. The sampling frame for the study included both landline and cellular telephones, increasing the effectiveness in reaching minorities and women of lower income, who are more likely to have only cell phones. The state of Virginia is fairly diverse in its population composition, and the survey was conducted in English and in Spanish to ensure inclusion of Hispanic women. The results were weighted to reflect the demographics of the target population, women residing in Virginia, ages 35 to 70, who have never been diagnosed with breast cancer. Virginia's mandatory breast-density notification law was in place for a year before the study was undertaken, so that this important background variable was held constant for all women in the study. The data reported here therefore give researchers a new and clearer picture of the state of knowledge about breast density among the broad population of women subject to current breast cancer screening recommendations.

One important result of this study is that the Virginia breast-density notification law seems to be effective in generating notifications: about half of the women who have had a mammogram in the past year report that their health care provider has informed them

about the density of the breasts. This is notable because the Virginia law requires notification to women whose breasts are dense, but does not mandate any notice to women with low breast density. Since notification is required only for women found to be in one of the two reportable dense categories, heterogeneously dense or extremely dense (categories that encompass about half of all women getting mammograms), this is about the percentage one would expect to be receiving notification. Those who had their last mammogram more than a year before the survey (i.e., before the notification law went into effect) are far less likely to say they have ever been notified, a fact which underscores the efficacy of the notification law. These results suggest that women who receive these notifications are taking due notice, and that some women who would never have received the currently required notice are nevertheless being informed about their breast density.

However, the results show that being notified about breast density does not equate to understanding what breast density implies in terms of mammographic sensitivity or breast cancer risk. While two-thirds of women are at least slightly familiar with the term ‘breast density,’ this superficial familiarity does not translate into knowledge of what breast density implies for a woman’s risk. Fewer than one in a hundred women spontaneously mentioned breast density as a risk factor for breast cancer when asked to name risk factors. Under more direct questioning, about one in five women understands that tumors are harder to detect in a woman with dense breasts, while only about one in eight (13%) understands that breast density raises a woman’s risk of getting breast cancer. The movement to notify women about their breast density assumes that, given better information, women will make better choices about prevention and monitoring of their health. These results show, however, that merely informing a woman about her breast density is not enough information in itself. The results point to a need for much broader efforts to raise awareness among women of what breast density implies for their cancer risk and their choice of screening practices.

The survey shows, not unexpectedly, that knowledge about breast density is unequally distributed across the population of women. Not surprisingly, women who see themselves as having higher risk for breast cancer and those who are otherwise well informed about breast cancer are somewhat better informed. A woman’s level of education is a strong predictor of her knowledge level. In contrast to earlier, small-sample studies that suggested equal levels of knowledge among black women as compared with white women, this survey shows that black women in Virginia are less knowledgeable about breast density than whites, and that this difference is lessened but remains statistically significant when socio-economic status is statistically controlled. This finding suggests the need for educational programs and educational materials that are culturally appropriate for African-Americans and outreach efforts that are targeted to reach that population. The survey results include the unexpected finding that Ashkenazi Jewish women in Virginia, an urban group high in education and socio-economic status, are less well informed about breast density than one would expect based on their demographic characteristics. This finding cries out for follow-up, perhaps with targeted qualitative research, and for additional efforts to bring information about breast density

to this group, who could easily be reached via liaison with Jewish religious and community institutions.

The multivariate results also show that women who have been informed by their health care provider about their breast density are more knowledgeable about breast density. However, the main effect of notification is on simple familiarity with the term “breast density.” The effect of notification on knowledge of breast density’s relationship with breast cancer is much more modest. This result reinforces the idea that notification laws are only a first step in what needs to be a broader campaign of education about what breast density (or absence of breast density) actually means for a woman’s health.

While the results reported here point to the need for better education and outreach, there are significant obstacles that will complicate a woman’s attempts to apply her knowledge about breast density. The survey reported here also included questions about whether women would be willing to change their breast cancer screening regimen if they knew more about their breast density and their risk for breast cancer. Those results will be reported elsewhere (22). Most states still do not require notification to women whose mammograms indicate high breast density, and women with low-density breasts are generally not notified of that fact, which could be of importance to them. Only a few states with density legislation also have mandates for insurance companies to pay for any secondary testing (23, 5), but for those states which do not have mandates, women who need the additional tests may end up going without since some supplemental tests are not yet covered by insurance (23, 11).

While the current survey represents a distinct advance in its coverage of a diverse, general population with probability sampling methods, it would be useful to survey a national sample of women, or to compare one or more non-notification states with these results for Virginia. The one published national survey of breast density awareness (12) relies on women pre-recruited on an access panel. Because panel members have repeated experience in responding to surveys, it is possible they respond differently to survey questions than do women in the general population. (24) The findings reported here should also be augmented with further research into the kind of information and messaging that will best inform women about the implications of breast density and motivate them to take appropriate action based on knowledge of their own individual breast density status. The public health community is still only at the beginning stages of raising womens’ awareness, increasing understanding, and enabling women to apply their knowledge about breast density and its relationship to breast cancer risk as they make their individual decisions about their breast health.

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Figure 1. Risk Factors for Breast Cancer

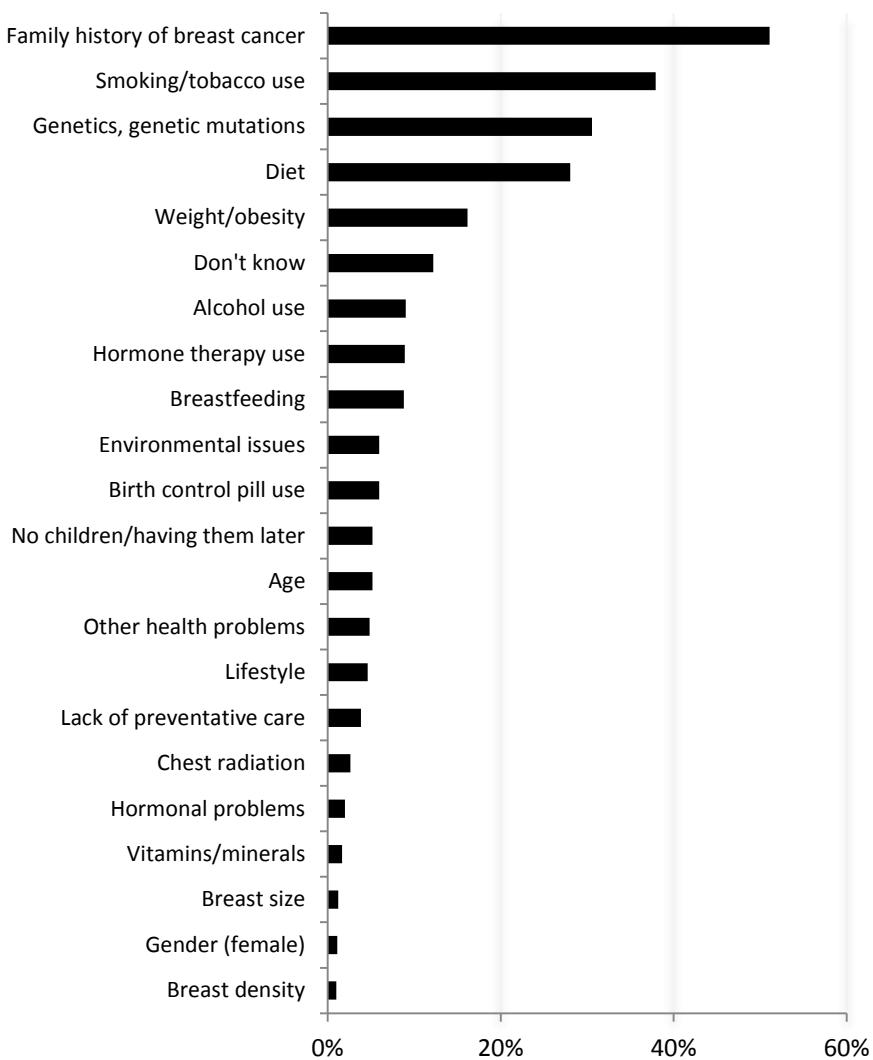


Figure 2. Accuracy of breast density knowledge

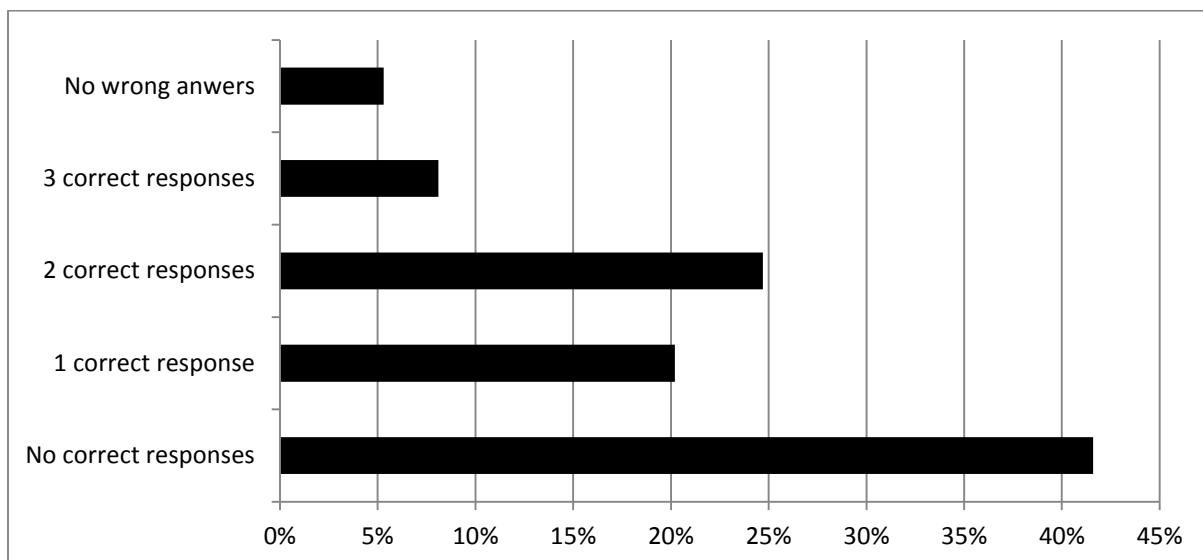


Table 1. Demographics and personal history of respondents

		N	%
Age	35-39 years	125	13.3%
	40-49 years	299	31.6%
	50-59 years	289	30.6%
	60-70 years	231	24.5%
Education	Some high school	41	4.2%
	High school diploma	263	26.9%
	GED	11	1.1%
	Some college	168	17.2%
	2-year degree	114	11.7%
	Technical or trade school	8	0.9%
	Bachelor's degree	209	21.4%
	Graduate or professional school	146	14.9%
Income	\$10,000-\$14,999	31	3.8%
	\$15,000-\$19,999	32	3.9%
	\$20,000-\$29,999	63	7.9%
	\$30,000-\$49,999	166	20.6%
	\$50,000-\$74,999	144	17.9%
	\$75,000-\$99,999	130	16.1%
	\$100,000-\$149,999	120	14.8%
	\$150,000+	92	11.4%
Race/Ethnicity	Hispanic	53	5.5%
	Ashkenazi Jewish	23	2.4%
	White only	751	76.8%
	Black or African American only	148	15%
	Asian only	22	2.3%
	Other or multiple race	57	5.9%
Marital Status	Married	623	63.0%
	Widowed	56	5.7%
	Divorced	160	16.4%
	Separated	34	3.5%
	Never Married	104	10.6%
Employment Status	Working full-time	502	54%
	Working part-time	100	10.7%
	Unemployed	59	6.3%
	Temporally not at work	13	1.4%
	Retired	157	16.9%
	Student	4	0.4%
	Homemaker/Stay at home mom	85	9.1%
Cancer Have you ever been diagnosed with cancer of any kind?	Yes	121	11.6%
	No	920	88.4%
Family Cancer History How many of your blood relatives have ever been diagnosed with breast cancer?	None	632	61.4%
	1	247	24%
	2	104	10.1%
	3	30	2.9%
	4	9	.9%
	5 or more	7	.7%
Parental Status Have you given birth to any children?	Yes	842	85.1%
	No	148	14.9%

Tobacco Use	Current smoker or tobacco user	186	19.1%
Have you ever used tobacco products, either now or in the past?	Smoked in the past	219	41.7%
	Never smoked	566	58.4%

Table 2. Being informed of breast density by date of last mammogram.

Time of last mammogram	Less than 1 year ago	1-2 years ago	3-4 years ago	5 or more years ago	Never had a mammogram	All women
Percent ever informed by doctor about density of their breasts	51.8%	33.7%	25.7%	24.0%	13.0%	38.8%

Table 3. Bivariate Correlations with Three Indicators of Breast Density Knowledge

Variable	Familiarity with Breast Density (1 - 4 scale)	Heard of Relationship between Breast Density and Breast Cancer	Accuracy of Knowledge about Breast Density (0 – 4 points)
Ashkenazi Jewish	-.335	-.135*	-.473
Asian	-.456	.088	-.265
Black/African American	-.358*	-.137**	-.328*
Hispanic	-.371	-.015	-.411
Other Race	-.249	.030	-.179
Age	.015**	.003	.013**
Education Level	.094***	.029***	.103***
Employed	-.195	-.028	-.087
Given Birth	-.187	-.102	-.171
Home Ownership	.558***	.111*	.604***
Household Income	.117***	.024*	.128***
Married	.159	.034	.112
Resident of Underserved Region	-.215	-.117**	-.250
Smokes Currently	-.363*	-.052	-.466**
Smoked in the Past	-.107	-.025	-.117
Informed About Breast Density by Doctor	1.228***	.322***	1.011***
Perceived Relative Risk of Breast Cancer	.187***	.052**	.206***
Familiarity with Other Cancer Risk Factors	.526***	.100***	.375***
Familiarity with Screening Recommendations	.451***	.124***	.441***

N of cases

934

910

942

* P-Value < .05

** P-Value < .01

*** P-Value < .001

Table 4. Multivariate Analysis of Three Indicators of Breast Density Knowledge

Predictor Variables	Dependent Variables		
	Familiarity with Breast Density (1 - 4 scale)	Heard of Relationship between Breast Density and Breast Cancer	Accuracy of Knowledge about Breast Density (0 – 4 points)
Ashkenazi Jewish	-.418**	-.172**	-.555***
Asian	-.526*	.084	-.369
Black/African American	-.272*	-.108*	-.236
Hispanic	-.138	-.001	-.208
Other Race	.111	.119	.180
Age	.007	.002	.008
Education Level	.046*	.020**	.055*
Employed	-.115	.001	-.026
Given Birth	-.114	-.095	-.105
Home Ownership	.202	.041	.265*
Household Income	.014	-.014	.026
Married	.041	.034	-.016
Resident of Underserved Region	-.053	-.081	-.089
Smokes Currently	-.248	-.023	-.333
Smoked in the Past	-.033	.002	-.050
Informed About Breast Density by Doctor	1.090***	.291***	.840***
Perceived Relative Breast Cancer Risk	.107**	.032	.154**
R-squared	.354	.170	.244
N of cases	934	910	942

* P-Value < .05

** P-Value < .01

*** P-Value < .001

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Managing Tiled Images in Breast Density Measurements

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Managing Tiled Images in Breast Density Measurements

Abstract. Tiled images are sometimes obtained for women with large breasts, which is a limitation of receptor size. In this retrospective HIPAA compliant study, automated breast density measurements for tiled images are compared with full MLO and CC views. Women with tiled views between July and December 2007 followed by full views within 15 months were included. Volumetric breast density (VBD) for tiled MLO views had very good correlation with full views ($r = 0.88$), while correlation between tiled and full CC views was poor ($r = 0.31$). VBD for all women requiring tiled CC views was low (<10%). In conclusion, VBD measured from a tiled MLO view is a reasonable substitute for a full MLO measure. Attributable risk of breast density for women requiring tiled CC views may be sufficiently low compared other factors such as high body mass index.

Keywords. Breast density; Mammography; Measures; Risk Models

1 Introduction

Women with high mammographic breast density are at 4-fold higher risk for breast cancer compared with women with fatty breasts. Incorporation of breast density into a breast cancer risk model may improve accuracy of risk assessment. For optimal use in a risk model, the measurement of mammographic breast density must be automated, accurate, and reproducible.

Digital mammography receptors vary in size from 19 x 23 cm to 24 x 30 cm. Women with small to average sized breasts will typically have two views of each breast for a screening mammogram; craniocaudal (CC) and mediolateral oblique (MLO) views. However, many large breasts cannot be completely imaged on a small receptor. These women may require two or three images to completely visualize the breast tissue for each projection. Measuring breast density on these tiled images may or may not reflect density measures that would be obtained using a single image of the same breast. The goal of this study is to evaluate if the volumetric breast density (VBD) of tiled MLO or CC images may reasonably approximate the VBD of the full view.

2 Methods

This retrospective study was HIPAA compliant and approved by our Institutional Review Board. A waiver of consent was granted.

We performed a retrospective review of women who underwent mammography on a small image receptor between July and December 2007 at our screening facility to identify women with tiled images. The primary screening site at one author institution (xxx) added a large receptor mammography machine in 2008. Women with either

tiled CC or MLO images on a small receptor followed by a single projection image on a large receptor within 15 months were included in the study. Women with a full view obtained greater than 15 months later were excluded as there may be other reasons for changes in breast density such as normal involution. Breast density was measured on tiled and single projection images using a validated automated measurement software program (Volpara, Matakinia Ltd, Wellington, NZ).

3 Results

Over 1800 women underwent screening mammography on the small image receptor machine between July and December 2007. Of these, eight women with 15 breasts had tiled MLO views followed by a single projection MLO view on a large receptor within 15 months. Seven women with 14 breasts underwent tiled CC views followed by a single projection CC view on a large receptor within 15 months. Two of these patients were excluded; automated density readings could not be obtained as a skin line was not detectable on the images.

For the MLO views, VBD for tiled views ranged from 2.0 to 18.9% (mean 6.0%), while VBD for full views ranged from 2.5 to 17.2% (mean 5.9%). Correlation between tiled and full VBD was very good ($r = 0.88$) (Figure 1). Body mass index (BMI) for these patients ranged from 24.2 to 37.8 (mean 30.0).

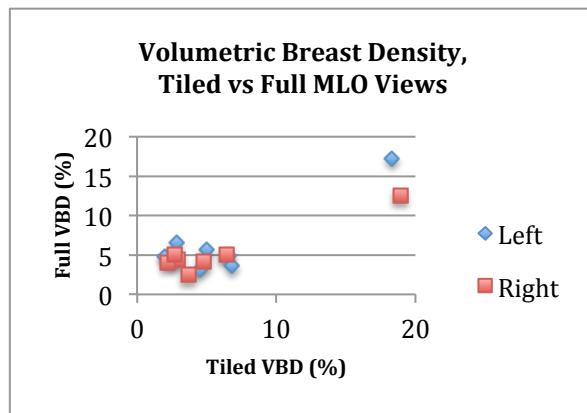


Fig. 1. Automated volumetric breast density of tiled versus full mammographic view for the left and right MLO views. Correlation is very good ($r = 0.88$).

As expected, total volume of the breast was lower for tiled views (range 725-1772 cm³, mean 1336 cm³) than full MLO views (range 856-2299 cm³, mean 1656 cm³) (Figure 2). The correlation is only good ($r = 0.71$).

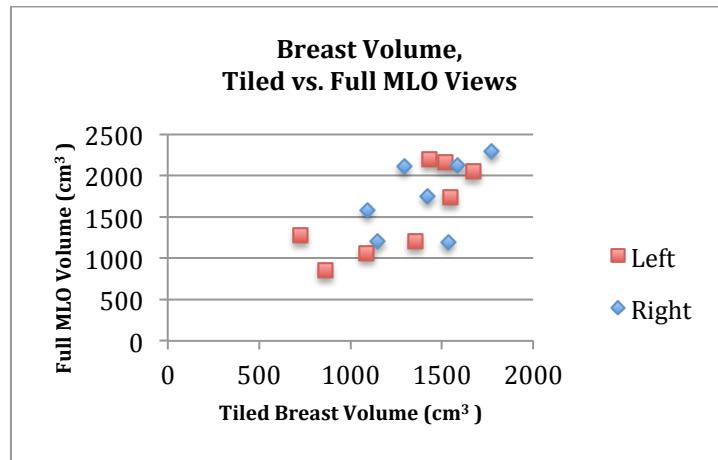


Fig. 2. Automated breast volume of tiled versus full mammographic view for the left and right MLO views. Correlation is good ($r = 0.71$), but lower than for VBD.

For the CC views, VBD for tiled views (range 4.0-10.1%, mean 6.9%) was similar to full CC views (range 1.9-7.6%, mean 4.5%). However, the correlation was poor ($r = 0.31$) (figure 3). Total breast volume results for tiled CC views (range 657-1846 cm³, mean 1129 cm³) were similar to results for full CC views (range 856-2123 cm³, mean 1262 cm³). Correlation for total breast volume was very good for tiled compared with full CC views ($r = 0.83$). BMI for these patients ranged from 23.5 to 37.8 (mean 29.3).

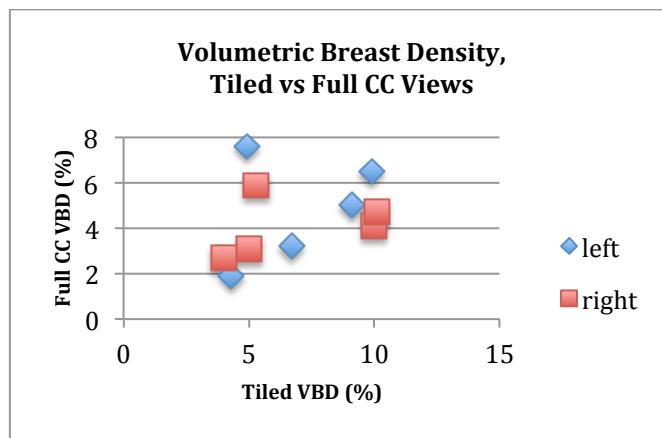


Fig. 3. Automated volumetric breast density of tiled versus full mammographic view for the left and right CC views. Correlation is poor ($r = 0.31$).

4 Discussion

The results of our study show that volumetric breast density measurements from MLO tiled images are relatively accurate compared to those obtained from a single projection image. A breast cancer risk model can therefore use a reading from a tiled MLO view as a substitute for a full projection image as a measure of breast density. The results for tiled CC views were not as promising as the correlation was poor between tiled and full views. Of note, however, is that the VBD for all CC views was low, less than 10%, which would equate to a lower risk population. Although the correlation was low, the absolute differences were small and likely clinically less important regarding breast cancer risk.

Most women with large breasts have a high body mass index (BMI). Mean BMI was in the obese and near obese range for the tiled MLO and CC patients respectively. Obesity increases the amount of fat in the breasts resulting in a lower percent breast density. Our study shows that the percent density for most women with large breasts is reasonably reflected with a low value using either a single tiled view or a full single projection view. Therefore, the use of an automated density measurement from a single tiled view is an acceptable alternative for inclusion in a breast cancer risk assessment model.

Incorporation of breast density into a breast cancer risk model must include adjustment for BMI. Obesity, like breast density, is also an independent breast cancer risk factor. Fatty tissue has high levels of aromatase, an enzyme that converts steroids to estrogens. Although women with a high BMI typically have a low percent breast density, their breast cancer risk may be more significantly driven by their obesity. Because BMI and breast density are independent breast cancer risk factors that can influence each other, the breast cancer risk associated with breast density must be adjusted for BMI.

Our study has limitations. Although the review included a large number of women, only a small number met inclusion criteria. A prospective study with a larger number of women may be helpful to confirm these results. A second limitation is the use of only one type of automated density software.

In summary, our study shows that an automated measurement of breast density using a single tiled MLO image may be an adequate reflection of the density obtained from a full mammographic image. The use of VBD from a tiled CC view may not correlate as well with VBD obtained using the full CC view. However, this may be less important given the overall low density of women requiring the use of tiled views. Breast cancer risk for these women may be driven more significantly by high BMI than dense breast tissue.